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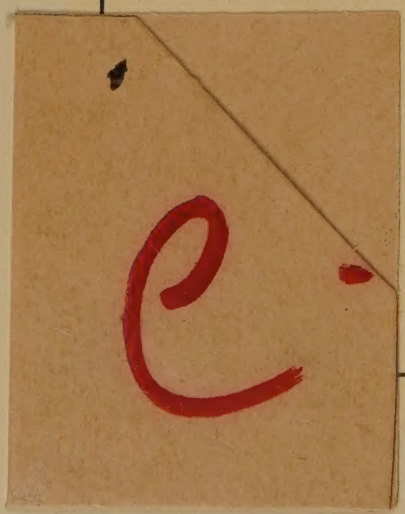

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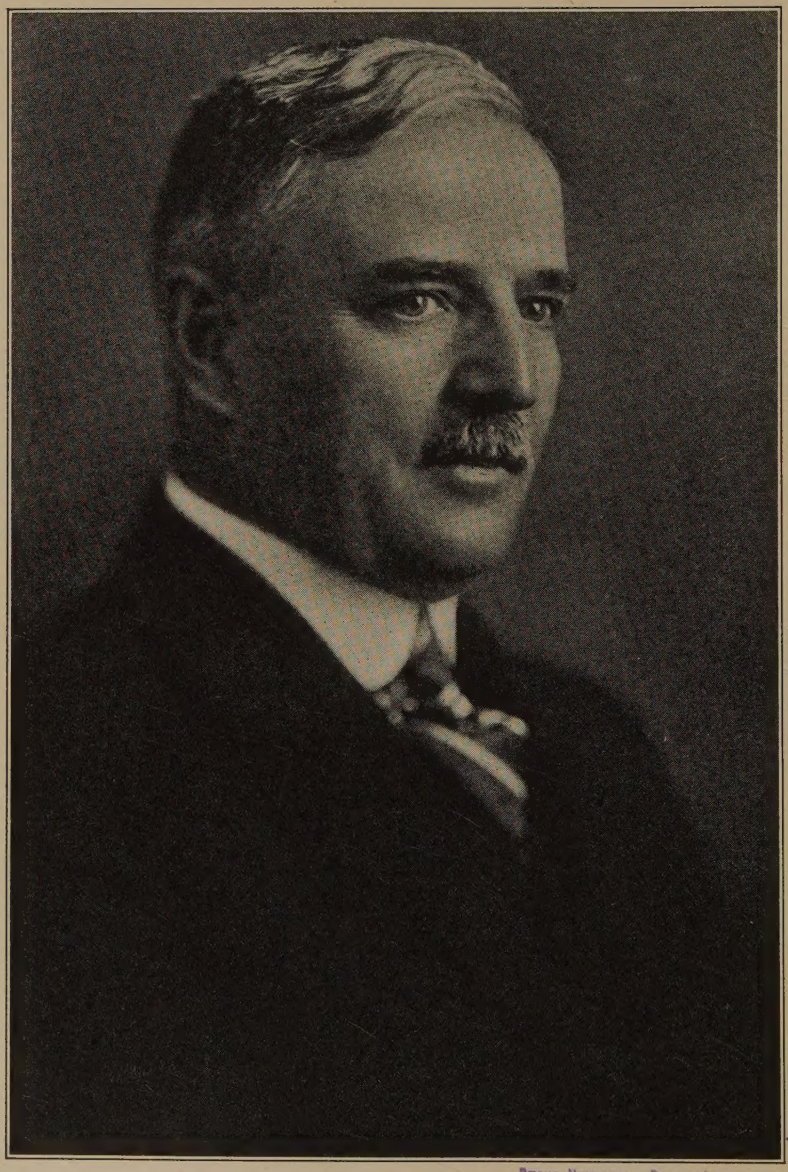

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HENRY JACKSON WATERS, LL.D.

GROWTH

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To the Memory of

HENRY JACKSON WATERS, B.S., LL.D.

Colleague and Pioneer
in the Experimental Study of Growth
This Volume
Is Affectionately Dedicated

Preface

THE series of popular lectures published in this volume was delivered under the auspices of the Missouri Chapter of the Sigma Xi during the Academic Year 1925-1926. The subject of Growth is one that has been given particular attention at the University of Missouri, and is one to which each of the collaborators of this volume has made original contributions. Dr. Jackson, now director of the Anatomical Institute at the University of Minnesota, was formerly a member of the Medical faculty at the University of Missouri, and began his researches on growth at that institution.

It is of course impossible in a series of five lectures to give an exhaustive discussion of growth. The aspects of the subject here presented have been selected with the aim of giving a comprehensive concept of growth. The introduction deals primarily with the nature of growth. The next three lectures discuss growth in its statistical, nutritional, and morphological aspects, respectively. The lecture on physiological regulation of growth closes the series. The illustrative material for each lecture is drawn chiefly from the field in which its author is primarily interested.

Bibliographies for individual chapters have been grouped at the end of the book.

H. D. HOOKER,
Secretary, Missouri Chapter,
Sigma Xi.

Columbia, Missouri.
June, 1927.

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Chapter I

Introduction

By William Jacob Robbins

Professor of Botany, University of Missouri

INTRODUCTION

GROWTH is an interesting subject because it is a personal subject. We have all grown. We may wonder at times why we have grown no more than we have or why we grew the way we did, but not many do more than wonder. Few of us attempt to learn what growth is, how it occurs, and why, or to answer any of the other fundamental questions we might ask about this process which we all experience.

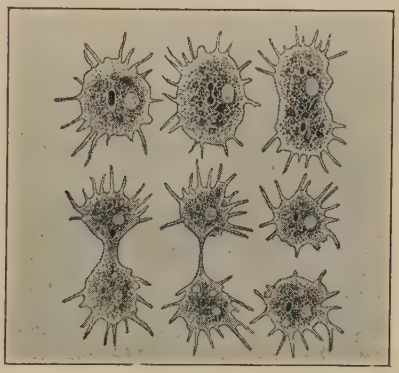


Figure 1. Amoeba polypodia in successive phases of division. The dark spot is the nucleus; the light one, a contractile vacuole. From Parker and Haswell's *Zoology*. By permission of the Macmillan Company.

What is growth? Most people would probably answer this question by saying that when anything grows it gets bigger. But that is evidently not all that we include by the term growth. A dog is not merely an enlarged puppy and a man is more than an overgrown infant. The body structure, proportions, and functions change as an individual grows. This phase of growth is commonly called differentiation or is referred to by the term development, and in all but the simplest living creatures it is intimately connected with increase in size.

We can illustrate what growth is by considering some examples. The amoeba consists of a soft bit of jelly, microscopic in size (from 0.03 to 0.3 mm. in diameter). Microscopic examination shows that this jelly, which is called protoplasm, consists of two distinct parts: a granular, almost transparent outer part which forms the larger portion of the amoeba and

which is commonly called cytoplasm, and a more or less spherical, somewhat grayish part, called the nucleus. Together these two parts comprise *a cell*. The amoeba lives in water and moves from place to place by a sort of flowing process. As the amoeba moves about in the water it flows around bits of plant or animal material, which are its food. If the food is sufficient in amount it grows larger, but not indefinitely. As the amoeba reaches a more or less definitely limited maximum size it separates or divides into two approximately equal parts, each with a nucleus and cytoplasm, which flow away as independent individuals capable of growing larger and dividing again. If the amoebae stuck together as they grew instead of separating and proceeding on their separate ways, a mass of jelly big enough to see with the naked eye would develop in time. Some organisms are like that. Those interesting creatures the slime molds, which may be found flowing over the surface and in the crevices of decaying wood or leaves, begin their lives as individuals much like the amoeba in appearance, size, and structure. As the slime mold grows the cytoplasm increases in amount and the nuclei divide. However, the new nuclei and their surrounding cytoplasms do not separate from one another and go their several ways, but remain together. Thus the slime mold gets larger and larger until it may consist of a mass of protoplasm several square inches in area.

Most living things with which we are commonly acquainted do not grow into mere masses of jelly as does the slime mold. They have leaves and roots and stems or legs and heads and eyes. This is something more than mere increase in size. This process which results in most organisms having definite shapes and parts we refer to as differentiation or development. In the amoeba growth is almost entirely increase in size.* The growth of

* Some creatures under certain conditions grow smaller. Thus a minute animal, the flatworm, if furnished with food will increase in size. If food is withheld it will grow smaller and smaller until it is a fraction only of its maximum size. Supplied with food it will again grow larger and so by controlling the food sup-

other living things may be almost entirely differentiation. In most cases, however, both occur together.

A description of the growth of a seed plant will help to make clear the way in which growth occurs, the way in which increase in size and differentiation take place.

A seed plant normally originates from a single cell in a part of the pistil of the flower. This cell is the megagamete or egg. It unites with a second, usually much smaller cell, the microgamete or sperm cell, the process of uniting being fertilization. The fused product of these two cells is the zygote or fertilized egg.* It is usually microscopic in size and structurally much like an amoeba, though not motile. The zygote increases in size, but not indefinitely. It soon divides into a chain of cells. One of these, the proembryo cell, differs from the rest in the fact that it continues its growth and forms the many-celled embryo plant.

ply the direction of growth may be reversed time after time. Many roots shorten or contract longitudinally and thus draw buds down into the soil. The small tubers of *Arum maculatum* which are found at a depth of 2 cm. are subsequently drawn into the soil to a depth of 10 cm. by a shortening of the root. Cells which have differentiated may under certain conditions dedifferentiate, that is, become embryonic again. It might be more accurate, therefore, to define growth as a change in size or differentiation rather than as an increase in them and to look upon it as a more or less reversible process. To be called growth the change should be more or less permanent. The change in size which a strip of potato undergoes when immersed in salt water or fresh water is not thought of as a growth change.

* Here at the very beginning of the growth of such a living thing we are faced by a problem, and the same problem exists for other living things which originate from a fertilized egg or zygote. As a general rule an unfertilized egg will not grow. Not until after it has joined with the sperm cell does it begin that ordered series of events which we call growth and which eventually result in the mature plant or animal. Why is this? What sort of influence does the microgamete exert upon the megagamete which starts it to growing? We cannot discuss these questions adequately here. We can only say that the eggs of some kinds of plants and some kinds of simple animals grow without being fertilized (parthenogenetically) and that the eggs of some other plants and animals which normally require fertilization have been stimulated by mechanical injury or by treatment with acids or solutions of various salts to growth without uniting with a sperm cell. Jacques Loeb succeeded by such artificial parthenogenesis in starting unfertilized frogs' eggs to grow and in producing a fatherless frog. See Lillie, *Problems of Fertilization*; Pearl, *Biology of Death.*

The proembryo cell divides in several planes, the number of cells and the size of the embryo plant increasing in the process. Some of the cells so produced form seed leaves, some a young stem, and some the beginnings of a root, the whole comprising an embryo plant which lies within the seed. Both increase in size and differentiation (increase in complexity) occur in this period of growth from zygote to embryo plant.

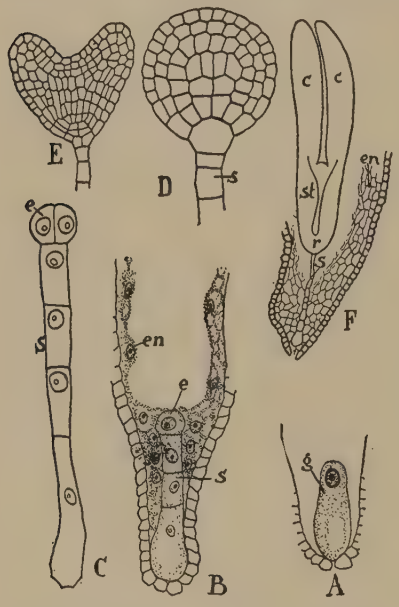


Figure 2. Early growth of a seed plant, the peppergrass (*Lepidium*). A. The single-celled zygote (*g*). B. The zygote has grown into a chain of cells, *s* is the suspensor and *e* the proembryo cell. C, D, and E. The further development of the proembryo cell into an embryo plant. The beginnings of two seed leaves are evident in E. F. A still later stage, the cells are not shown. Note the seed leaves (*c*) the stem (*st*) and root (*r*). From Curtis, Nature and Development *of plants.* By permission of Henry Holt and Company.

If we plant the seed it absorbs water and the food materials stored in the seed are digested. The cells of the embryo plant increase in size and number and the seedling bursts its way out of the seed, establishing its root system in the soil and its stem and leaves in the air. From this time on the growth is largely limited to particular parts of the plant body. A region consisting of a group of cells at the end of the main stem and of each branch and at the tip of each root and rootlet, grows. The growth of these regions results in increase in length and in the formation of leaves, flowers, fruits, and seeds. In addition, in plants such as our trees and many of our common herbaceous plants, a cylinder of tissue, the cambium, found between the wood and the bark, retains the power of growth. The growth of the cambium results in increase in diameter. A thin slice or section of the growing region of the root

tip or stem tip of a plant shows very beautifully the way in which growth takes place in each of these regions of the plant. Just above the root cap is the region where the cells increase in number by cell division. The cells here are much alike. They are small, thin-walled, polyhedral in shape, with nuclei large in proportion to the size of the cells. The new cells nearest the root cap continue dividing. We call these embryonic cells. Those which are further from the tip no longer divide, but increase considerably in size causing the root as a whole to lengthen. Those cells which have increased to near their maximum size are then transformed into their permanent form, assuming special shapes, wall modifications, and particular functions. As you can see from this brief description the growth of the single-celled plant, usually microscopic in size, into the many-celled plant occurs in three stages or steps. There is involved an increase in the number of cells by the process of cell division; there is some increase in size of the individual cells formed; and there is a differentiation of these cells into those which make up the leaves, flowers, fruits, seeds, wood, bark, and other parts of the mature plant. In the entire plant no one of the steps is necessarily completed before the next occurs. Although cell division and increase in size predominate in the earlier stages of growth all three may occur, in fact usually do occur, in different regions of one plant at the same time.

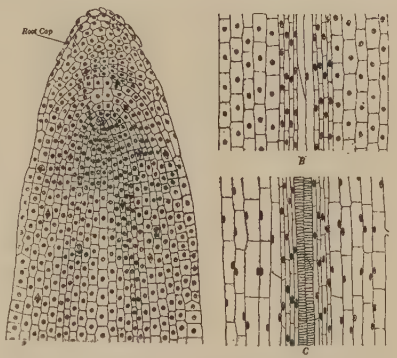


Figure 3. Portions of lengthwise sections of a sunflower root. A. The embryonic region and root cap. Note dividing cells in the embryonic region. B. In the region of elongation, 2 or 3 millimeters back from the root tip. Cells are increasing in size. C. In the region of differentiation. Cells are assuming permanent form. From *General Botany* by Smith, Overton, Gilbert, Denniston, Bryan, and Allen. By permission of the Macmillan Company.

It is by such a series of events that what was three thousand years ago a single cell, a bit of living jelly less than half the

size of a pinhead, grew into a giant Sequoia, which now stands on the California coast, with a trunk thirty feet in diameter at the base and towering three hundred feet into the air. During these three thousand years the original single-celled zygote has divided into an almost incalculable number of cells, for a cubic inch of Sequoia wood contains over one billion. During the same period differentiation resulted in the formation of the roots, the trunk, branches, needles, cones, and other parts which by their shapes and arrangements enable us to recognize this tree and enable the tree to continue its life and growth. Few of the innumerable cells which now make up the various parts of the mature tree resemble the ellipsoidal, thin-walled, colorless cell which was the zygote. At the stem tips and root tips and in the cambium layer there are still embryonic cells which continue dividing and which resemble in some respects the original zygote from which they came. The others have differentiated into cells with a variety of shapes, sizes, thicknesses of wall, types of content, and they now constitute the characteristic and functional units of the different parts of the tree.

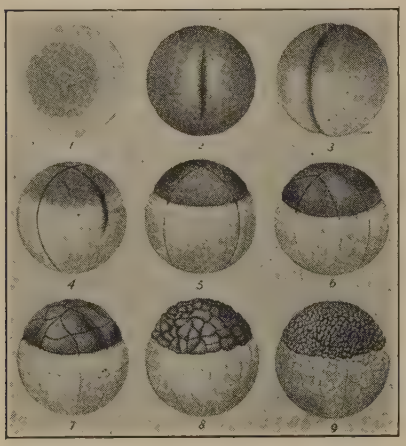


Figure 4. The growth of a salamander, *Amblystoma punctatum,* from zygote (No. 1) to many-celled sphere (No. 9). After Eycleshymer. From Minot's *Age, Growth and Death.* By permission of G. P. Putnam's Sons.

The vertebrate animal, in common with almost every other living thing, also originates as a single cell, the zygote or fertilized egg, which divides into many cells at first much alike in general shape and contents. In Figure 4 the early growth of a vertebrate animal, a salamander, is pictured. The first drawing represents the single-celled zygote, microscopic in size. At that

time of its life a salamander looks like the drawing and consists essentially of a nucleus, cytoplasm, and some food material. These parts are not shown in the drawing because it represents a surface view. The second drawing shows the beginning of the formation of a two-celled salamander which is completely formed in the third drawing. An eight-celled salamander is shown in the fifth drawing. In the ninth drawing the salamander consists of cells too numerous to count. The result of these divisions is the production of an ever increasing number of cells arranged in a sphere. Although the cells are much alike some differentiation has occurred, even in these early stages of growth. The cells differ in density of protoplasm, in size or color, in quantity of food material, and particularly in their later history. Some cells which can be recognized in these early stages by their position relative to other cells and by their contents form germ tissue, some form nerve tissue, and so on. The further growth of a vertebrate animal is too complicated for us to consider in detail here. It may be sufficient to say that the cells making up this sphere increase in number and differentiate by a regular progression of stages to form the mature individual. The increase in the number of cells together with the enlargement of the cells themselves results in an in-

Figure 5. Ten stages in the growth of a chick. Times of incubation are as follows: No. 1—20 hrs., No. 2—24 hrs., No. 3—2 days, No. 4—2 days, 19 hrs., No. 5—2 days, 22 hrs., No. 6—3 days, 16 hrs., No. 7—4 days, 8 hrs., No. 8—5 days, 1 hr., No. 9—7 days, 4 hrs., No. 10—8 days, 1 hr. After Franz Keibel. From Minot's *Age, Growth and Death.* By permission of G. P. Putnam's Sons.

crease in size and the differentiation results in the development from this many-celled sphere of the parts and organs with which we are familiar in the mature individual. This is shown in the series of drawings in Figures 5 and 6 which depicts the differentiation observable without detailed microscopic study in the growth of the chick. The drawings show none of the cells.

Figure 6. A chick removed from an egg which had been incubated 10 days and 2 hrs. After Keibel. From Minot's *Age, Growth and Death.* By permission of G. P. Putnam's Sons.

During the first twenty-four hours of incubation the young chick has grown far beyond the stage of growth comparable with the last drawing of the salamander in Figure 4. To the unaided eye it appears as nothing but a line on the surface of the egg yolk (1 and 2). During the second day (3) the head and heart have formed. During the third day (4 and 5) the eye and tail become visible. The fourth day (6) the beginnings of the wing and leg are discernible. These parts as well as others become more prominent the fifth day (7 and 8), the seventh (9), and eighth day (10), until by the tenth day (Figure 6) differentiation has proceeded far enough to permit anyone to recognize the birdlike characteristics of the creature.

Associated with the differentiation or development of the organs and parts of the body is a differentiation of the cells which compose them. They do not retain their embryonic appearance, but change in shape and contents and become specialized in function. Compare the differentiated cells from a mature animal (Figure 7) with the isodiametric embryonic cell.

Differentiation, which is the name we give to the phase of

growth which causes us to grow into the individuals we are and prevents us from being a mere mass of 160 pounds or so of quivering jelly, evidently follows a definite rule with each kind of living thing. The frog's egg always grows into a frog and not into a dog or chicken. Our noses always grow on the fronts of our faces and not between our shoulder blades. What causes differentiation? any kind of differentiation which saves us from

Figure 7. Nerve and muscle cells of animals. A, B, C, D, nerve cells. E, F, G, muscle cells. After Sharp. By permission of McGraw-Hill Book Co. These are mature differentiated cells.

the fate mentioned above? and what (in the second place) causes it to follow a definite rule? Why do we always grow two arms and not six or seven? and why do we grow hair on the tops of our heads instead of the soles of our feet? These questions cannot be completely answered. One answer is that there is a vital force or principle which guides and shapes the clay of which we are made. This force is supernatural. It is "some all-controlling, unknown and unknowable, mystical, hyper-mechanical force." We cannot study it because it is supernatural, beyond the limits of inquiry by natural means to which we as natural and not supernatural beings are limited. The common

biological answer is *heredity*, which, as the word is commonly used, means in plain language that our fathers were made that way before us and we are made like them. A more correct answer is that the particular cell from which each of us starts, using the word "us" in a broad biological sense to include every living individual, has a particular kind of living stuff carrying

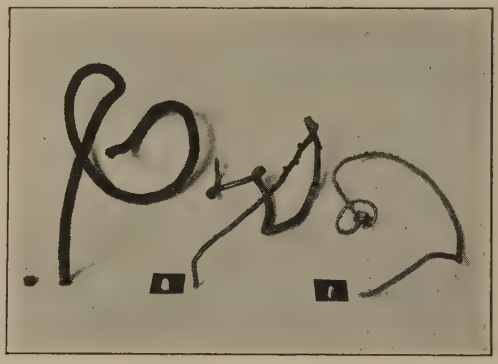


Figure 8. Pharaoh's serpents. An "egg" similar to that from which each "serpent" grew is shown at the left of each of the serpents. The shape of the "egg" and its composition, one of them containing a black material in addition to mercury sulphocyanate, cause the differences in color and form.

on a particular series of chemical reactions and physical processes which work out into the characteristic structure of the individual.

We might use an analogy to make this point of view clearer. Suppose we take a small cone of mercury sulphocyanate and set fire to the tip. The burning compound forms a long serpent-like ash a hundred times or more the volume of the original cone. This is the familiar firework called Pharaoh's serpent. The growth of Pharaoh's serpent depends upon the particular kind of material of which the cone is made. To have a cone of charcoal, sulphur, or gunpowder will not do. It must be mercury sulphocyanate. It depends also upon the chemical reactions which this stuff carries on. Only burning (oxidation) will form

the snake. Other types of reactions such as reduction or combinations with other compounds than oxygen will not produce the same result. Even though a cone is made of mercury sulphocyanate and that cone is burned a serpent will not be formed unless the cone burns from the tip. It must not burn at the same rate on all its surface else some other kind of monster will grow out of it. This means that certain physical conditions also must be met. So the scientist pictures the growth of a zygote into an individual as depending upon a particular kind of living stuff carrying on a particular series of chemical reactions and physical processes which work out into the characteristic structure of the individual.* The chemical constitution of the living stuff in a zygote is, of course, much more complex than that of the mercury sulphocyanate in the cone and the chemical reactions and physical processes concerned in the growth of a zygote into the simplest creature are infinitely more numerous and complicated than those which take place in the oxidation of the sulphocyanate.

The discoveries within the last decade of the remarkable influence of the secretions of various glands upon differentiation in animals are a wonderful and fascinating record of the progress in our knowledge of differentiation. Wonderful as these discoveries are they are but a beginning. They do not tell us much of the differentiation in the many living things which have no such glands nor the causes of the differentiation in the glands themselves.

You can readily perceive, however, that the statement that growth takes place by a division of cells, an enlargement of the cells so produced, and a differentiation of these cells into permanent form is only a skeleton outline of the process of growth.

Cell division, as it usually occurs, is a complex process, particularly for the nucleus. The series of drawings in Figure 9 il-

* These chemical reactions and physical processes may be modified by the external environment just as the burning of the mercury sulphocyanate may be affected by the character of the gas supplied.

lustrates the division of a plant cell. In its essential features it is identical with the division of animal cells. Notice that the nucleus fragments into a number of rods, the chromosomes, which by a regularly occurring series of events are equally distributed to the two new, or daughter, cells where they are reorganized into approximately spherical nuclei. The result of cell division is the formation of two cells from one, each of the new cells possessing a nucleus in which there is half of the substance of the chromosomes formed from the original nucleus. This marvelous and complicated process, repeating itself time after time with wonderful precision, occurs whenever a new cell is formed and takes place in the larger plants and animals millions of times during their growth from a single cell to a mature individual. An average-sized potato, such as you might eat for dinner, has between five and six billions of cells. Cell division must have occurred in its growth between five and six billion times, each time without an error. The fundamental cause of cell division is evidently an important problem from the standpoint of growth because the increase in the size of organisms is due to an increase in the number of cells rather than to increase in the size of the cells themselves. The cells in a tomato plant are about the same size as those of a pine tree. The cells in a pine tree one foot high are about as large as those in

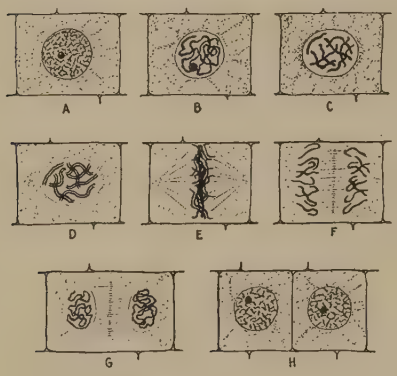


Figure 9. Semi-diagrammatic representation of the division of a plant cell. A. Resting cell, the chromatin of the nucleus in a fine network. B. The chromatin is gathered into a long thread. C. This thread breaks up into rods—the chromosomes. D. Each chomosome splits lengthwise. E. The nuclear membrane disappears and the split chromosomes are arranged in a plane across the equator of the cell. F. The chromosome halves separate, one complete set (eight in this case) going to one end of the cell and the other set to the other end. G. and H. Each group of chromosomes is reorganized into a new nucleus and a cell wall forms which results in the formation of two new complete cells. After Sinnott. By permission of McGraw-Hill Book Company.

a pine one hundred feet high. The cells of the mouse are not very much smaller than those of the elephant.

The increase in the number of cells, the increase in the size of the individual cells, and their differentiation require the construction of additional protoplasm, the construction of cell walls, the construction of the materials of bones, of shells, carapaces, hair, finger nails, and so on. These are made from the food materials which the organism uses. The beef and bread and butter we eat today becomes living protoplasm or bone or hair tomorrow. This is a complex process. The food must first be digested, broken up into simpler parts in somewhat the same way that the construction of a new building from an old one requires that the old one be first torn to pieces. The process of digestion deserves more attention than we can give it here. How the chemical changes involved in digestion are accomplished was a mystery until it was discovered that those catalytic agents, the enzymes, make them possible at the relatively low temperatures and slight acidities or alkalinities found within the bodies of living organisms. Mr. Pecksniff, in *Martin Chuzzlewit*, appreciated this remarkable discovery. "The process of digestion, as I have been informed by anatomical friends, is one of the most wonderful works of nature. I do not know how it may be with others, but it is a great satisfaction for me to know, when regaling on my humble fare that I am putting in motion the most beautiful machinery with which we have any acquaintance. I really feel at such times as if I was doing a public service. When I have wound myself up, if I may employ such a term," said Mr. Pecksniff, with exquisite tenderness, "and know that I am Going I feel that in the lesson afforded by the works within me I am a Benefactor to my Kind."

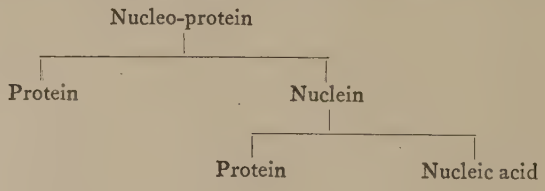
The products formed by the digestion of the food are built up into the complex chemical compounds which constitute the protoplasm and other constituents of the body. Body construction from digested food by the amoeba or the slime mold which have no cell walls, no bones, nor hair, nor teeth, but only pro-

toplasm, would appear to be relatively simple. However, when we realize that the construction of the protoplasm of the slime mold from the water, mineral salts, and digested wood upon which it lives is really the making of living material from non-living stuffs we see that it is not so simple. An acquaintance with the chemical constitution of what appear to be the important constituents of the slime mold also emphasizes that fact. The following table presents the results of a chemical analysis made by Lepeschkin of a slime mold.

CHEMICAL COMPOSITION OF PLASMODIUM OF SLIME MOLD

	Per cent	
Water	82.6	
Dry matter	17.4	
Monosaccharids	14.2	Organic matter soluble in water. (40.7)
Protein	2.2	
Amine bases, purin bases, asparagin, etc.	24.3	
Nucleo-proteids	32.3	Organic matter insoluble in water. Chief fundamental material of protoplasm. (54.9)
Free nucleic acid	2.5	
Globulin	0.5	
Lipoproteids	4.8	
Neutral fat	6.8	
Phytosterin	3.2	
Phosphatide	1.3	
Other organic material (polysaccharids, pigment, resin)	3.5	
Ash about half extractable by water	4.4	

The nucleo-proteids would seem to be the most important part of the protoplasm since they constitute about one-third of all the dry matter and about three-fifths of the dry matter which does not dissolve in water. Nucleo-proteins are chemical compounds with large and complex molecules. They appear to be constructed of proteins and nucleic acid since they yield those substances when they are decomposed by hydrolysis.



The proteins are complex compounds of high molecular weight. They are built up of amino acids. The simplest formula for oxyhemoglobin, a protein of the red blood corpuscles, is $C_{658}H_{1181}N_{207}S_2FeO_{210}$ equivalent to a molecular weight of 15,455. Compare this with a formula of $C_{12}H_{22}O_{11}$ and a molecular weight of 342 for cane sugar.

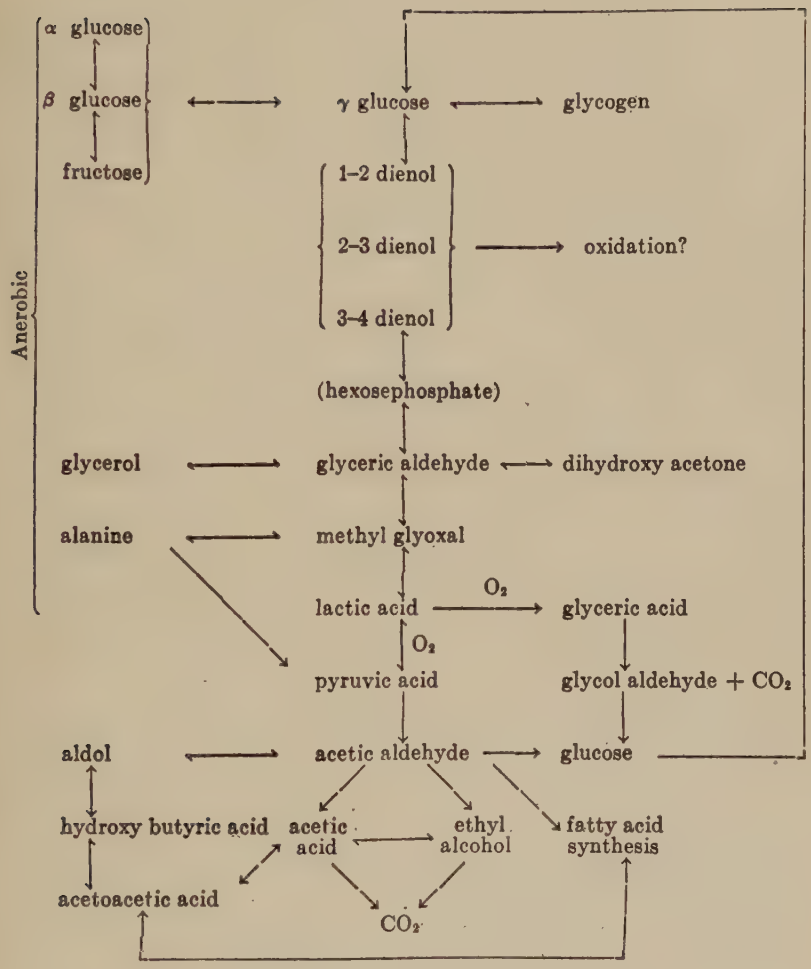
Nucleic acid also is a chemical compound with large molecules. It appears to be built up of sugar, phosphoric acid, and certain nitrogenous bases. The formula for yeast nucleic acid is $C_{35}H_{49}O_{29}N_{15}P_4$, equivalent to a molecular weight of 1303.

It is evident, therefore, that even in an organism where growth appears to be a simple process it is a very complex one and one with which we are not yet fully acquainted. The biologist assumes for his working plan that the construction of living protoplasm and other body parts takes place according to known or discoverable laws of physics and chemistry. Parts of the process can be imitated in a test tube, but its entirety remains a secret, possibly one which we may never discover. We must agree with Aristotle when he says, "Wherefore one should not be childishly contemptuous of the most insignificant animals, for there is something marvelous in all natural objects."

The questions raised in the discussion of growth thus far would appear to make the problem of growth sufficiently complicated, but there is still another important essential in the process. The construction of new protoplasm, new cell walls, and new body parts requires energy in somewhat the same way that energy, in the form of muscular work by masons, is necessary for the construction of a brick house from bricks. The energy used in growth is that present in the food materials. It is set free by their destruction in a manner somewhat similar to the way in which the energy in coal is set free in its destruction by burning. We call the process by which a living organism sets free the energy stored in food materials respiration, and for most plants and animals oxygen from the air is used in respiration, and water and the gas carbon dioxide are formed. In such

an organism as the slime mold not all of the food materials absorbed are built up into protoplasm; a part of them is destroyed, yielding energy for the building process, and their material constituents are given off by the slime mold in the form of carbon dioxide and water. In motile organisms much of the energy resulting from respiration goes for work, and in warm-blooded animals like man a considerable part goes for the maintaining of body temperatures. The destruction of the food materials in this process of respiration is also a complicated affair as is evident from the scheme on the opposite page arranged by Shaffer. This shows in outline form what probably happens in the destruction of glucose in the body.

Since growth involves either increase in size or increase in differentiation or both, the measurement of growth should consider both of these phases. We can measure increase in size. One way to do this is to measure increase in volume. This is sometimes difficult to do and we therefore frequently use one dimension such as height as a measure of growth. Since increase in size usually involves increase in weight, growth is frequently measured by taking weights. Differentiation, on the other hand, is difficult to express in units. The result is that our measurements of growth are usually concerned with one phase of growth, namely, that which involves increase in size or something related to it. Measured by increase in length, the most rapid growth I am acquainted with is that of the Philippine bamboo, which has been reported as growing eighty-two feet in three months, over eight inches a day. Measured by increase in volume or mass, those microscopic plants, the bacteria, and the microscopic animals, the protozoa, grow most rapidly. Under favorable conditions bacteria may double their volume in nineteen minutes. Both the rapidity and the total amount of growth are influenced considerably by age, heredity, food, including the accessory foods (the vitamins), mineral salts, temperature, water, light, toxic materials, the development of various parts of the body, and other factors.


α glucose
β glucose
fructose
γ glucose
glycogen
1–2 dienol
2–3 dienol
3–4 dienol
oxidation?
(hexosephosphate)
glycerol
glyceric aldehyde
dihydroxy acetone
alanine
methyl glyoxal
lactic acid
O₂
glyceric acid
O₂
pyruvic acid
glycol aldehyde + CO₂
aldol
acetic aldehyde
glucose
hydroxy butyric acid
acetic acid
ethyl alcohol
fatty acid synthesis
acetoacetic acid
CO₂
Anerobic

In the simpler organisms the rapidity of growth under uniform external conditions may be almost constant, but with the more complex plants and animals growth varies in rate with age. This is a familiar fact. Young animals and young plants grow rapidly, but as they approach maturity growth of the plant or animal as a whole ceases, although some growth probably continues in some parts as long as the individual remains alive. Even in man growth of new blood corpuscles and the growth of new tissue to cover a wound occurs in the aged, and hair and finger nails may grow somewhat after death. The curve in Figure 10 illustrates the cessation in growth in length as the sunflower becomes mature. Growth of man plotted in the same way would produce much the same kind of curve though the units would be different. What causes this limitation in growth is a very interesting question. Why don't we continue growing forever? In annual plants such as the sunflower the cessation of growth is associated with the onset of reproduction—formation of flowers, fruits, and seeds. In perennial woody plants eventual cessation of growth in height is partly due to difficulties incident to supplying sufficient water to the top of the tree as well as to other causes. In animals the problem is a very complex one. There is apparently no inherent reason why an animal should cease growing, because tissues, for example those of the heart, which cease growth when they reach normal size in an animal body, may be kept growing indefinitely if removed while young from the body and cultivated in a sterile fluid. This is called tissue culture. The development of toxic mate-

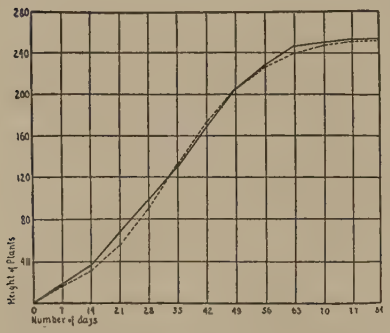


Figure 10. The height of the sunflower plant, *Helianthus,* from planting to maturity. Note that growth in height ceases as the plants approach maturity. After Reed and Holland. By permission of National Academy of Sciences.

rial, the exhaustion of some essential growth material, and other hypotheses have been offered. The problem is further complicated by the fact that in most vertebrate animals there are more or less sharply marked growth cycles, periods in which growth speeds up and then slows down.

Heredity is an important determiner of growth in both plants and animals. A mouse will never grow to be as large as an elephant even if we feed it on hay and peanuts. In Figure 12 we have a striking example of heredity as a determiner of growth. The plant on the left is a dwarf corn plant, the one on the right is a plant of the common type of corn. They have grown side by side in a field. Nothing we can do with the dwarf plant will make it grow higher. By limiting the water, mineral salt supply, light, and other factors in the external environment we could limit the height which the normal plant would make to that of the dwarf. The effect of external factors such as those mentioned above on the growth of plants is nowhere more strikingly shown than in the dwarf trees produced by Japanese gardeners, who grow in a flower pot a pine tree eighteen inches high but two hundred years old.

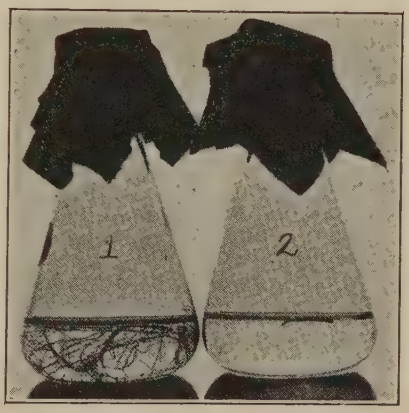


Figure 11. Growth of an isolated corn root tip. The root tips are maintained under sterile conditions in a nutrient solution. The one on the right is supplied sugar. The one on the left has none. This is a "tissue culture" experiment with a seed plant. After Robbins. By permission of the University of Chicago Press.

The effects of water, temperature, and toxic materials are more marked in their effects upon the growth of plants than they are on most animals. The water supply is particularly important for the growth of plants. This is because increase in the size of cells in plants is largely due to absorption of water (in animals it is largely due to increased construction of proto-

plasm), and because plants evaporate large quantities of water from their broad expanse of leaves. A date palm may lose in this way from 100 to 190 gallons of water in a day and an ordinary corn crop absorbs through its roots and loses through its leaves in the course of its growth enough water to cover the ground on which it grows to a depth of seven inches. The result is that the effective water supply—difference between water absorbed and water lost—is one of the most important factors in plant growth.

Figure 12. A dwarf and normal variety of corn grown side by side. After Kempton. Courtesy of the *Journal of Agricultural Research.*

The absorption of the water results in the development of a pressure in plant cells. This is frequently considerable in amount. In 1874 at Amherst, Col. W. S. Clark surrounded a developing squash with an iron harness provided with a lever attachment and found that the squash, which weighed forty-seven and one-half pounds at the end of the experiment, raised a weight of five thousand pounds. The experiment attracted considerable attention at the time and one highly respected minister of the gospel advised his congregation, "If God in his providence has given such enormous power to a squash to overcome difficulties, how much more will He give you the power to overcome the difficulties that may be in the way of your reaching the true end of living."

Temperature is another important factor for plant growth and for the growth of cold-blooded animals. It is not so im-

portant for warm-blooded animals. Toxic materials often in very minute amounts retard the growth of plants. One part of the gas ethylene, a constituent of illuminating gas, in ten million parts of air is sufficient to retard the growth of sweet peas and some other plants. The growth of higher animals is also influenced by poisons, but animals are less likely to come in contact with them than plants.

A supply of mineral salts is important for the growth of both plants and animals. Plants require salts of potassium, calcium, iron, magnesium, sulphur, phosphorus, and possibly traces of manganese, boron, and zinc. Animals require sodium chloride and compounds of calcium, iron, potassium, magnesium, iodin, phosphorus, sulphur, and possibly others. Compared to the total weight of the body the amount required of any one of these elements is very small. All of the iron contained in a corn plant is less than is contained in two ordinary needles, yet the absence of this small quantity of iron completely prevents the growth of the plant. The reason for the importance of some of these mineral elements is fairly completely known. The significance of others is only guessed.

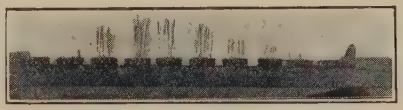


Figure 13. The effect of temperature on the growth of wheat. The pots are placed in a trough heated at the left end and cooled with ice at the right end. The temperature increases, therefore, from right to left. After Ganong. By permission of Henry Holt and Company.

Light is an important factor affecting the growth of both plants and animals. For green plants light is necessary for the construction of food from the elementary substances carbon dioxide and water. It also has other effects upon the growth of plants. Everyone has seen the elongated plants with white or yellow color and small leaves which grow in the dark, for example, the sprouts from a potato tuber. Not so many are acquainted with the remarkable effect which the relative length of day and night has upon the differentiation of flowers by plants. Some bloom best when the days are long and the nights

are short, and will not flower when the days are short and the nights are long, but continue to increase in length of stem and number of leaves. Others blossom only when the days are short. Tobacco, at least certain varieties, is such a plant. The plants shown in Figure 14 were grown in a greenhouse in the winter when the days are short. The plant on the right was also exposed to electric light from sunset to midnight. This plant has been grown under such long days to a height of over fifteen feet without the production of flowers. The importance of ultra-violet light in the growth of animals is now well known. In the absence of ultra-violet light the pathological condition known as rickets develops. Cod-liver oil or similar material containing the necessary vitamin may be substituted for it.

Figure 14. Both these tobacco plants were grown in a greenhouse during the winter. The plant on the left was exposed to the natural winter daylight. The plant on the right received in addition to daylight, electric light from sunset to midnight. This variety exposed to long days will grow 15 feet or more in height. After Garner and Allard. Courtesy of the United States Department of Agriculture.

Food sufficient in both quantity and quality is needed. The term food is used here to refer to the carbohydrates, fats, and proteins. The quantity of food needed is usually measured in calories. A three-year-old child needs food equivalent to about 1000 large calories a day, a fourteen-year-old child needs 1800, a full-grown man, 3000-3500 calories. These calories may be supplied by any one of the three foods mentioned above or by a mixture of them. In addition, however, to the quantity of food attention must be paid to the quality. Green plants make their own food materials from the elementary materials, carbon dioxide, water, and inorganic nitrogen, for example, nitrates or ammonium salts. Animals, however, are unable to do this and must be supplied with both carbon and nitrogen in organic com-

bination. If we ate only carbohydrates and fats, which contain no nitrogen, and in addition some nitrates or ammonium salts, we not only would not grow, but would gradually starve to death because of our inability to build up the complex nitrogen-containing compounds necessary for the building of new cells and for the replacement of old cell parts. What are the simplest forms and the smallest number of kinds of organic nitrogen-containing compounds necessary for the building of new cells and for the replacement of old cell parts? What are the simplest forms and the smallest number of kinds of organic nitrogen required for animals? This question is a very important one. It is like asking what sort of bricks are necessary for constructing a certain kind of house. The animal must be supplied with the right kind of bricks, the green plant makes it own.

Figure 15. The effect of long days and short days on the growth of the coneflower (*Rudbeckia*). Seed sowed December 19. The plant at the left received, in addition to daylight, electric light from sunset to midnight. The plant at the right received 7 hours' illumination only. Photographed May 14. After Garner and Allard. Courtesy of the United States Department of Agriculture.

Even though sufficient food of the right kind, together with water and mineral salts, are supplied, growth will be markedly interfered with unless the food contains those interesting accessory food materials, the vitamins. Of unknown chemical composition and needed in very small amounts, they are likely to be overlooked, with unfortunate effects on growth. Most plants seem to construct their own vitamins and they are therefore directly or indirectly the source of the vitamins for animals. In some cases traces of organic matter have a marked effect upon the growth of green plants.

The development of one part of the body has a considerable influence on the growth of the rest of the organism. The effect of pinching off flower buds or young fruits on the growth of the balance of the plant is well known. The development in animals of various glands such as the thyroid gland, suprarenal,

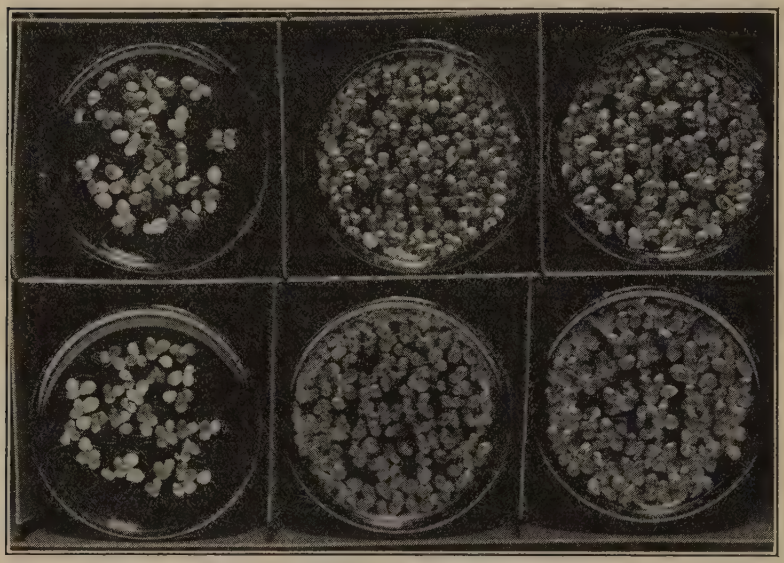


Figure 16. The effect of minute amounts of organic matter upon the growth of a green plant. Left—growth of duckweed in a mineral nutrient solution. Center—growth in same solution plus 4 parts per million of extract of autolyzed yeast. Right—growth in same solution plus trace of extract of peat. After Saeger.

pancreatic, pituitary, and sex glands have remarkable effects upon growth.

There is much more that could be said regarding growth and in the following sections various phases of the subject which have been sketched here will be elaborated. The process of growth is a wonderful and remarkable one even in the meanest and humblest of living creatures. No matter how small we are or how poorly our features are collected on our countenances we should never be dissatisfied. We should never regret that we

have not attained the stature of a Hercules or the features and form of a Venus. We should feel astonished and thankful that we ever grew at all and that our features are recognizable as those of the human race.

Chapter II

An Analysis of the Course of Growth and Senescence

By Samuel Brody

Professor of Dairy Chemistry, University of Missouri

AN ANALYSIS OF THE COURSE OF GROWTH AND SENESCENCE

I. Introduction

GROWTH and senescence take place simultaneously. We grow and grow old at the same time, and there is, therefore, no dividing line between the two. It is only a question of dominance. Roughly, during the first third of our life, up to about twenty-five years of age, growth changes predominate, while during the last two-thirds of life, the changes of senescence predominate. Before describing each of these two phases separately, it seems advisable to obtain a bird's-eye view of the life cycle as a whole, and to describe the several stages of the life cycle.

The best verbal description of the age changes in man is no doubt that penned by Shakespeare. Shakespeare distinguishes seven stages.

> At first the Infant,
> Mewling, and puking in the Nurses armes:
> Then, the whining Schoole-boy with his Satchell
> And shining morning face, creeping like snaile
> Unwillingly to schoole. And then the Lover,
> Sighing like Furnace, with a wofull ballad
> Made to his Mistresse eye-brow. Then a Soldier
> Full of strange oaths, and bearded like the Pard,
> Jelous in honor, sodaine and quicke in quarrelle,
> Seeking the bubble Reputation
> Even in the Canons mouth: And then, the Justice
> In fair round belly with good Capin lin'd,
> With eyes severe, and beard of formall cut,
> Full of wise sawes, and moderne instances,
> And so he playes his part. The sixt age shifts
> Into the leane and slipper'd Pantaloone,

With spectacles on nose, and pouch on side,
His youthful hose well sau'd, a world too wide,
For his shrunke shanke, and his bigge manly voice
Turning againe toward childish treble pipes,
And whistles in his sound. Last scene of all,
That ends this strange eventful historie,
Is second childishnesse, and meere oblivion,
Sans teeth, sans eyes, sans taste, sans everything.

We shall follow the example set by Shakespeare and empirically divide life into seven stages. Instead, however, of beginning with the infant stage of life, we shall begin with the ovum, that is, the egg after fertilization.

There is no doubt but that the most marvelous changes of the whole life take place during the earliest stage of life, namely, the embryonic stage. This stage comprises in man the first three months of life. During this stage, the ovum, a single cell of less than one seven-hundredth of an inch in diameter has been developed into a body containing practically all the important structures found in adult man. Indeed, during this stage the embryo contains some structures not found in adult man as, for example, gill slits in the third week, and tail in the sixth week.

The embryonic stage is followed by the fetal stage lasting from the age of three months to the age at birth, which is between nine and ten months after fertilization of the egg. During the fetal stage, the parts already formed during the embryonic stage grow in weight and maturity, but no new parts are formed.

Up to the time of birth the embryo, and then the fetus, obtains nourishment and oxygen by way of the umbilical cord from the mother's blood by means of a structure known as the placenta (an outgrowth of the outer, or chorion, membrane surrounding the embryo), which is attached to the mother's womb. At birth this method of obtaining nourishment and oxygen is abruptly ended. The newly born infant must

obtain the oxygen directly from the air by means of its lungs and the food by means of its mouth, stomach, and bowels. This revolutionary change in the mode of nutrition affects but slightly the course of growth. There is a loss of weight for about three days, probably largely due to the fact that the milk flow is not properly established for several days following parturition, then growth is in full swing again. The infantile stage embraces the first two years after birth, that is, up to the time the milk teeth come into place.

The infant stage is followed by the fourth, or juvenile, stage lasting from about three years up to about twelve years in girls and fourteen years in boys. We have examined a large number of growth curves and have found that during this stage growth in weight proceeds at the constant rate of about 9 per cent per year. Thus, if a child weighs 40 pounds, he gains about 9 per cent of 40 or 3.6 pounds per year; if he weighs 70 pounds, the gain is about 9 per cent of 70 or 6.3 pounds per year, and so on. The fact of growth at a constant rate from 5 to 15 years is illustrated in Figure 17.

Figure 17. Growth of well-nourished children from 5 to 18 years. In the case of these well-nourished children, growth between 5 and 15 years takes place at a constant percentage rate, namely, 9.6 per cent per year, that is, the body weight is doubled once in 7.2 years. In the case of poorly nourished children, the percentage rate of growth is accelerated at the time of puberty.

Then follows the fifth stage, that of adolescence, with the wonderful unfolding of the masculine or feminine personality. Overnight the youth is metamorphosed into a man or a woman.

The advent of the adolescent stage in girls is marked by the appearance of the phenomenon of menstruation, usually appearing between the ages of thirteen and fourteen years, de-

velopment of pelvis and mammary glands, and growth of hair on the pubes. In boys it is marked by the appearance of pigmented hair in the pubic regions and on the face, and the "breaking" and then deepening of the voice. Simultaneous with these changes there occurs, under certain conditions of nutrition, an acceleration in growth in weight and in height, changing from a gain of 9 per cent per year to a gain of, perhaps, 12 per cent per year, depending on nutritive conditions.

While there is no direct evidence to this fact, it seems reasonably certain that the acceleration in growth at this age is associated with the development of the sex function. This idea is inferred from the fact that emasculated children do not show some of the changes associated with puberty, and from the results obtained by Edgar Allen, the anatomist at the University of Missouri, and by other investigators, who found that substances from several genital tissues injected into spayed animals produced an accelerated growth of certain tissues. However, this accelerated growth initiated at puberty does not last very long. About two years after the onset of puberty, the rate of growth rapidly decreases, and by the age of about twenty-two years growth in weight and height is practically completed.

The age of twenty-three, at any rate, marks the end of our physical growth. There is no doubt that from the standpoint of physical strength we are at our best between twenty and thirty years of age. The proof of this statement is furnished by Figures 18 and 19 and by the fact that it is between these ages that championships are generally held in such of the competitive sports which require great sudden physical exertion as, for example, prize fighting.

From thirty years on, the decline in the physical powers is unmistakable. The age of fifty usually marks the termination of the phenomenon of menstruation and consequently the end of the reproductive period in woman. In man the reproductive period is not terminated as abruptly as in woman, but the decline is unmistakable from about thirty-five years on. The de-

clining physical powers in man are usually accompanied by several external manifestations in the secondary sex characteristics. One of these is an increasing tendency to corpulence after the age of thirty-five. The increasing tendency to fattening in emasculated animals is a well-known phenomenon. Another external sign of declining sex powers is the appearance of coarse hairs on the face and body. Stockard makes the following remarks concerning the increased hairiness in man after thirty-five: "On first thought one might consider him to have fully arrived at the completely developed male state. This is not correct, however, since the gonads of such an individual have actually begun to decrease in the sexual power. The coarse hair growth is a plumage expression resulting from a decline in the male gonadial activity rather than the attainment of its zenith." Stockard thinks that the development of the characteristic plumage in the Golden Seabright Bantam rooster after castration is comparable to the growth of the coarse hair in man with the decline in his reproductive powers. The reproductive period in man may be considered as practically at an end at the age of sixty. The period between twenty-five and fifty or sixty may, therefore, be considered as the sixth or middle life stage.

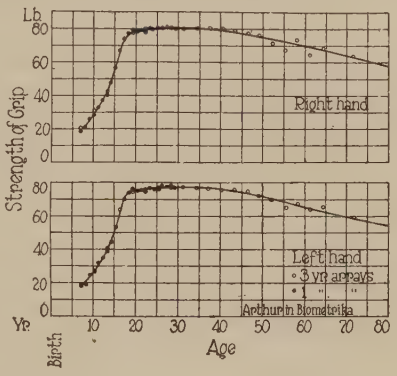


Figure 18. Age changes in the strength of grip. The curves show that we are at our best in this respect between 20 and 30 years.

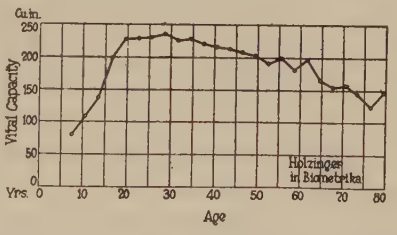


Figure 19. Age changes in vital (lung) capacity. The curve shows a distinct decline in vital capacity after the age of 30 years.

The seventh and last stage follows the age of sixty.

The immediate mechanisms regulating these remarkable changes with advancing age are not clear. We do, however, have some theories which are very helpful in visualizing and "explaining" the processes and which, for this reason, deserve some consideration.

We may first consider the problem of growth in bulk. Growth in bulk is largely due to the increase in the number of cells in the body, and the problem is, therefore, reduced to a consideration of the phenomenon of division of cells. Why do cells divide? We have no ultimate answer to this question. We can only explain this phenomenon in a figurative way by means of an analogy. The *fact* is that when a young cell such as a young bacterium or cell from the body of an animal is placed in an appropriate nutrient medium, such as blood serum, it grows in size. Why does it grow in size? Here the theory begins. Our theory is that it grows in size because it is in an unstable equilibrium with the medium surrounding it, and growth is therefore an expression of a tendency on the part of the cell to reach stable equilibrium. The chemist, and the physicist, constantly uses this idea of equilibrium in explaining what are known as kinetic and dynamic processes, that is, processes involving changes. As soon, however, as the cell reaches a certain size, it becomes unstable with respect to its size, and this unstability is made good by dividing. As soon as the cell divides it becomes young again and unstable with respect to the medium surrounding it and so it increases in size again. The cell is thus always in an unstable equilibrium either with respect to the medium or with respect to its size, and our explanation is that this unstability is the immediate cause of increase in the number of cells and consequently in the bulk of the body of the organism.

An experimental illustration of this theory of unstable equilibrium, but as related to a whole organism, was recently furnished by Child. He found that a planarian, a species of flatworm, may be made, so to speak, to grow forward or backward,

that is, it may be made at the will of the investigator to grow old or "grow" young. This is accomplished by regulating the food supply. On increasing the food supply, it increases in size and assumes the characteristics of the adult animal; in brief, it grows old. On decreasing the food supply, it decreases in size and it assumes the characteristics of the young, immature animal: it "grows" young. In this way these animals may be made to oscillate indefinitely between the states of blessed youthfulness and ripe maturity. Employing the terminology of the chemist, growth is a reversible process as illustrated diagrammatically in Figure 20.

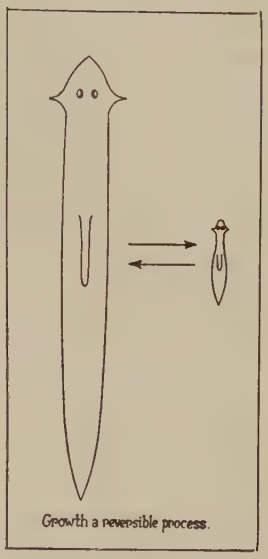


Figure 20. Growth is a reversible process as indicated by the fact that certain animals may be made to assume the juvenile or adult stage at will by regulating the supply of the substratum (food) of the growth reaction. This figure is based on Child's investigations.

We can find a physical analogy to this periodic growth and division of cells in the periodic movements of a pendulum. The pendulum is vibrating in its tendency to reach a place of rest or equilibrium, which it cannot find in the absence of retarding forces such as friction, and so *potentially* a pendulum is capable of indefinite vibration when once started. Cells in the body are also *potentially* capable of indefinite growth and division, and growth of cells in the body stops only on account of retarding influences developed in the body in the course of growth.

The proof of the theory that cells are potentially capable of indefinite growth and division and that the cessation of growth and termination in death are due to some retarding factors developing in the nutrient medium in which cells grow, was furnished experimentally by several investigators.

The first proof of this theory was furnished by Leo Loeb,

pathologist of the Washington University, St. Louis. Leo Loeb found that cancer cells, which are merely modified body cells, can be grown indefinitely when transplanted successively from old to young animals. This led to the conclusion that cancer cells must be considered as potentially immortal, and Loeb generalizes this for all forms of somatic cells of multicellular animals.

Further experimental proof of this theory was furnished by cultivating body cells outside of the body, or *in vitro*, as it is called. Leo Loeb was the first to discover that it is possible to grow tissues *in vitro*. To Ross G. Harrison of Yale University, however, is due the credit for developing practical methods of tissue culture *in vitro*, and to Alexis Carrel of the Rockefeller Institute is due the credit for developing the method of cultivating tissues *in vitro* indefinitely by a process of continuous irrigation.

In 1913 Doctor Carrel cut out a piece of tissue from the living heart of a chicken and placed it in a continuously irrigated nutrient medium in a glass dish. This strain of tissue is still living, and it grows now as well as it did in 1913, doubling itself in bulk about every twenty-four hours. Now, since in the chicken's body growth continues only for about a year and it begins to slow down almost immediately after development of the chicken's body begins, while *in vitro* it grew at an undiminished rate for thirteen years, the obvious conclusion is that *in vitro*, where the nutrient medium is kept at a constant composition by continuous irrigation, cells are capable of indefinite growth and that the decline and final cessation of growth in the body are due to some changes with advancing age in the nutrient medium surrounding the cells in the body. The results of Carrel's investigations thus furnish a complete proof of the theory that body cells are potentially capable of indefinite growth.

Indefinite growth, of course, implies an indefinite life, that is, physical immortality, for the phenomenon of aging or senescence and consequently physical death, is no doubt associated

with cessation of growth. The results of Carrel then lead to the conclusion that body cells are not only potentially capable of indefinite growth, but they are also potentially immortal, and that cessation of growth, and death, is due to the finite nature of the universe in which the organism or tissue finds itself.

Having obtained some insight into the mechanism of simple growth in bulk, we may mention the mechanisms of differentiation. We have divided the life cycle into seven stages (there may be many more), and each stage is characterized by some special feature. The adolescent stage, for example, is characterized by an acceleration of growth in stature, weight, etc. By what mechanism are these changes brought about? The theory of these changes is even less clearly understood than the theory of growth in bulk. We are inclined to the belief that these changes are brought about by substances of the nature of hormones. The tissues from the following glands may be mentioned as possibly producing differentiating hormones: thyroid (the thyroids, which weigh from one to two ounces, are situated on each side of the windpipe); hypophysis, or pituitary glands (situated at the base of the skull); pineal gland (situated at the base of the brain behind and above the pituitary); and the sex glands. A detailed consideration of these, and other hormone-producing glands and their activities will be found in Dr. Green's lecture of this series.

The three mechanisms of growth explained above, namely, the inherent force residing in cells to grow indefinitely, the growth-retarding influences resulting from the finite universe in which the cells or organisms find themselves, and the hormonic mechanisms, are the internal factors of growth. There are many external factors regulating growth, such as climate and food supply. We shall assume in this discussion that the external factors are optimal. The effects of food supply on growth are discussed by Dr. Hogan in another lecture of this series.

In the above discussion, we have attempted to present the

qualitative aspects of growth and the general mechanisms of growth in words. We now proceed to a consideration of the *quantitative* aspects of growth and aging, that is, a consideration of growth and senescence which can be represented by numerical values and curves. Before presenting these curves it seems desirable to say a few words in explanation concerning the general spirit in which the curves were prepared.

The curves were prepared, first, in order to give a quantitative picture of the changes with age as contrasted to the qualitative ideas one obtains from a verbal description, and, second, in order to obtain the *laws* of growth. Now, in a scientific sense, a law is usually a mathematical formula which describes quantitatively a large number of phenomena, thus recognizing their essential similarity. The meaning of the idea of law may be best illustrated by reference to Newton's law of gravitation. Newton's law of gravitation is merely a statement of the fact that the force of attraction between two bodies is proportional to the product of their masses, and inversely proportional to the square of the distance between them. This statement is presented in the form of the formula

$$F = G\frac{MM'}{d^2}$$

in which F is the force of gravitation, M and M′, the masses of the bodies, and d the distance between the bodies. G is a proportionality constant known as the constant of gravitation.

This formula represents a great law because it shows the element of sameness in such diverse phenomena as the fall of the apple, the movement of the tides, and motions of the heavenly bodies. Thus, by the discovery of this law, a great many apparently unrelated phenomena were shown to be the consequences of the same force—the force of gravitation. This formula does not, however, explain the ultimate nature or meaning of the force of gravitation. This is true of most other scientific laws—they represent the quantitative aspects of the phenomena in a generalized form; they show by their form the similarities be-

tween the phenomenon under consideration and other phenomena, but they do not give the ultimate nature or meaning of the phenomenon.

In preparing this set of curves of changes with age we have kept in mind the idea, not merely of giving a quantitative picture of the age changes, but also of discovering a law of growth which should indicate the similarity between the course of growth and the course of physico-chemical changes outside of the body. This attitude of comparing growth to a physico-chemical process seems to be legitimate in view of the fact that growth is by definition a physico-chemical process—certain substances typical of foodstuffs are obviously converted during the course of growth and senescence into other substances typical of the body tissues and fluids. Of course, growth is not merely a physico-chemical reaction, but it is conceivable that in spite of all the complexities of growth there may be one reaction which dominates the course of growth during each phase of growth. The fact that the secretion of one gland such as the thyroid or pituitary can dominate the course of growth is good substantiating evidence of the theory that the course of growth may be controlled by the slowest or limiting reaction. That one reaction may, and usually does, limit the course of a complex chemical process is a well-known principle in chemistry.

II. The Curve Representing the Life Cycle

The purpose of this section is to attempt to derive a law of changes due to age including the whole of the life cycle. Figure 21 shows the changing resistance with age against fatal pneumonia. We see the curve rising up to the age of thirteen years, that is, up to the age of puberty. The resist-

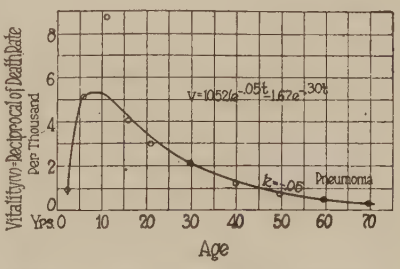


Figure 21. Age changes in resistance to fatal pneumonia. The smooth curve represents the formula on the chart; the circles are observed values.

ance against pneumonia is greatest at this age, that is, there are fewer deaths due to pneumonia at the age of thirteen than during any other age. After the age of thirteen, the resistance to pneumonia declines. A man of forty-five is seen to have approximately the same resistance as a child of three years, and has only about 11 per cent of the resistance possessed by a child of thirteen years. At seventy, we can see the resistance against pneumonia to be only 2 per cent of the resistance of a child of thirteen.

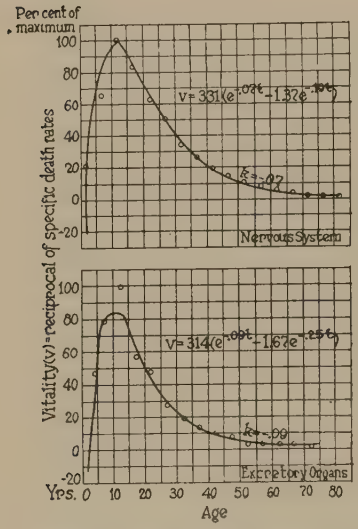


Figure 22. The rise and decline of vitality with age as measured by the reciprocals of mortality due to the breakdown of the nervous and the excretory systems.

The formula on the chart gives a quantitative statement of the course with which the resistance to pneumonia changes with age. The exponent in the first term of the formula multiplied by 100, that is 5.0, is the percentage decline per year in resistance to pneumonia beginning with the age of fifteen years.

The curve gives us a fair idea of growth and senescence as measured by the rise and decline of resistance to pneumonia with age. The formula representing the rise and decline of this curve would be considered as a law comparable, for example, to the law of gravitation if the curve were obtained on a homogeneous population and if the formula were shown to have some universal significance. But, of course, this curve was not obtained on a homogeneous population. The individuals included in the census were of many different types, some possessing a vigorous constitution and high resistance to pneumonia, others weak and of slight resistance to pneumonia. As a result there was a selective action, a weeding out of the less fit individuals, and the curve, for this reason, is not a strictly accurate

representation of the changing vitality with age. Indeed, it seems to have certain features of a probability curve. But it is, nevertheless, a useful curve giving us a bird's-eye view of the age changes.

The curves in Figure 22 similarly represent the changing resistance with age against death due to breaking down of the nervous system and of the excretory system. Here again the maximum resistance is at thirteen years which is represented by 100 per cent. The resistance is then seen to go down, in the case of the upper curve, to 73 per cent at twenty years, 30 per cent at thirty years, 20 per cent at forty years, 10 per cent at fifty years, 5 per cent at sixty years, and about 1 per cent at eighty years. From the formula on the chart, after the age of fifteen years, the resistance declines at the rate of 7 per cent per year. In the lower curve, the vitality declines at the rate of about 9 per cent per year.

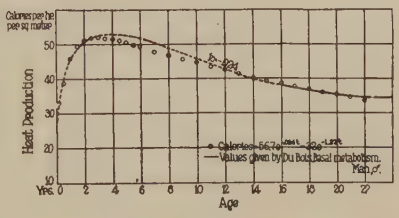


Figure 23. The rise and decline of basal metabolism with age. The area referred to in the chart was obtained by Meeh's formula. The numerical values are tentative as neither the areas nor the values for metabolism were definitely established.

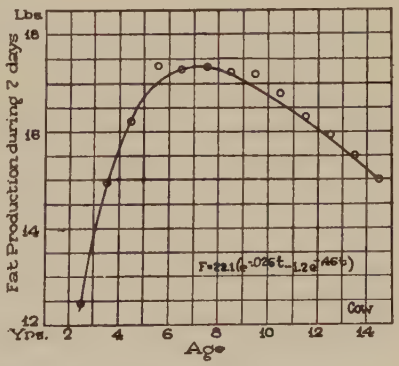


Figure 24. The rise and decline of milk production in Holstein-Friesian cattle.

Figure 23 shows the rise and decline of basal metabolism per unit area with age. The basal metabolism per unit area appears to be at a maximum at the end of the infantile period, namely, at two and one-half years, then it declines at the rate of about 2 per cent per year.

Figure 24 exhibits the rising and declining curves of vitality with age in another animal form, namely, the dairy cow, and as

measured by her capacity to secrete milk. The milk is seen to reach a maximum between seven and eight years. This is also the age when the body weight is at a maximum. The milk flow then steadily declines.

These figures indicate that while the processes of growth and senescence are probably simultaneous, and that while it is true that "we begin to die the very moment we are born," there are, nevertheless, two more or less distinct phases: a phase of growth during which growth is predominant, and a phase of senescence during which the process of senescence is predominant.

In harmony with the idea expressed in the preceding section that the course of growth and senescence may be limited by a chemical process, the equation chosen to fit these curves is one resembling in form, at least, a certain type of chemical process, namely, two simultaneous consecutive monomolecular reactions.

III. The Curve Representing the Course of Senescence and Its Equation

Having obtained a view of the life cycle as a whole, we may now consider in greater detail that phase of the age curve during which the process of senescence predominates, and if possible, obtain an equation or law relating the degree of senescence with age.

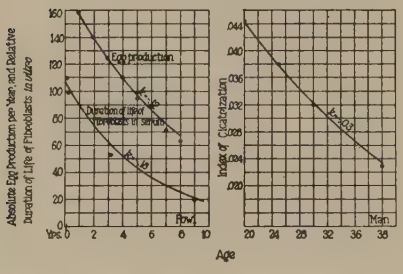


Figure 25. The course of senescence in the domestic fowl as measured by the decline in egg production, and by the decline in growth-sustaining powers of its serum. Also the course of senescence in man as measured by the decline in the speed of healing wounds of a certain size with advancing age. (The age curves for healing of wounds and growth of fibroblasts in serum were constructed on the basis of data published by Carrel and coworkers.)

Figure 25 shows the course of senescence in the domestic fowl as measured by the decline in egg production with age and by the decline in growth-sustaining powers of its serum. The circles represent the observed values. The egg production per year is seen to decline from 158 in the first

year to 63 in the eighth year. The smooth curve was drawn on the assumption that the egg production declines by 12.3 per cent per year; that is, that each year's production is 87.7 per cent of the production during the preceding year. As far as this particular group of birds is concerned, it is evident that the law of senescence as measured by the decline in egg production is that the increase in senescence, or decline in vitality, takes place at a constant rate, namely, at a decline of 12.3 per cent per year. The data on which Figure 25 is based are given in Table I.

Table I

THE DECLINE IN EGG PRODUCTION WITH AGE IN THE DOMESTIC FOWL

Age in years	*No. of birds included*	*Egg production per year. Nov. 1 to Nov. 1*	
		*Observed**	*Calculated†*
1	222	158	158.5
2	221	140	140.1
3	222	124	123.9
4	222	110	109.6
5	193	95	96.9
6	28	89	85.7
7	27	71	75.7
8	6	63	67.0

Figures 26 and 27 indicate respectively, the course of mortality in man due to different diseases, and the course of mortality in a population of the fruit fly *Drosophila*. In these figures the scale of ordinates is divided in a geometrical progression and whenever a set of changing values falls on a straight line on this paper, then it is obvious that the change takes place in a geometrical progression, in other words, at a constant percentage rate—for, by definition, a geometrical progression is

* The observed values are averages of two breeds and eight different groups of birds kept under different conditions of management. To save space in this general publication, the individual records, and their significance, are omitted.

† Calculated from the equation $y = 179.2e^{-0.12t}$ in which y is the yearly egg production at the age t. The egg production during any year is 88 per cent of the preceding year's production.

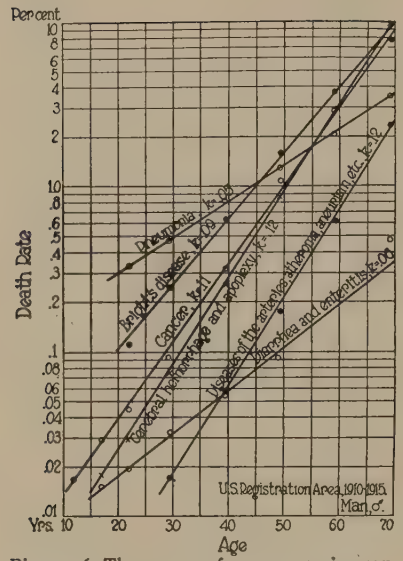


Figure 26. The course of senescence in man as measured by the increase in percentage mortality with increasing age. The distribution of the data points on a straight line indicates that the percentage mortality increases at a constant percentage rate. The values of k when multiplied by 100 represent percentage mortality.

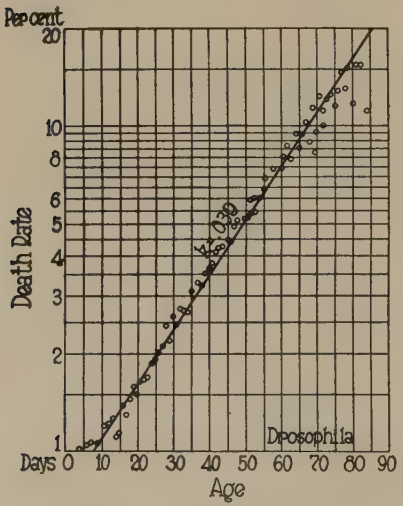


Figure 27. Percentage mortality of the fruit fly (*Drosophila*) at various ages. Plotted from data by Pearl and coworkers.

one in which each term bears a constant ratio (= relative rate) to the preceding term. It is evident from these figures that the law governing the course of mortality of man after the age of about fifteen years is the same as the law governing the course of mortality of the fruit fly *Drosophila* after the age of ten days. Indeed, by proportioning the axes in an appropriate manner, the two sets of curves can be made to coincide as shown in Figure 28.

By way of summary of this section, we may say that from the available data it seems that the descriptive law of the course of declining vitality is that the degree of senescence increases, or the degree of vitality decreases with age at a constant ratio, indicated by k on the charts.

This statement may be put in the form of a formula and, in our judgment, it promises to become a law of senescence. The constancy of rate is the fundamental feature characterizing the process. In man the constancy of the rate of senescence begins to apply at the age of about twenty years;

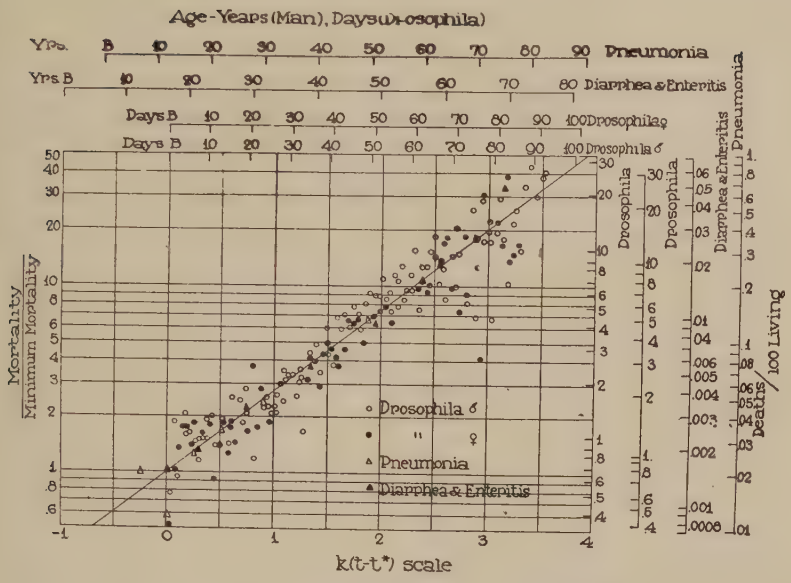

Age-Years (Man), Days (Drosophila)
Yrs. B 10 20 30 40 50 60 70 80 90 Pneumonia
Yrs. B 10 20 30 40 50 60 70 80 Diarrhea & Enteritis
Days B 10 20 30 40 50 60 70 80 90 100 Drosophila ♀
Days B 10 20 30 40 50 60 70 80 90 100 Drosophila ♂
Mortality
Minimum Mortality
Drosophila ♂
" ♀
Pneumonia
Diarrhea & Enteritis
Drosophila
Drosophila
Diarrhea & Enteritis
Pneumonia
100 Living
Deaths
k(t-t*) scale

Figure 28. In this chart the mortality curves of man and fly (Figures 26 and 27) were made to coincide.

in the fruit fly *Drosophila* at about ten days of age; in the dairy cow at about seven years; in the domestic fowl at about one year. The mathematical equation of this statement of the course of declining vitality with age is

$$V = Ae^{-kt}$$

or

$$S = Ae^{kt} \qquad (1)$$

in which V is the index of vitality, S is the index of senescence, t the age, e the natural base of logarithms, and 100k is the percentage rate. This is also the equation used to represent the decline in the velocity of a chemical reaction with time, which is in harmony with the idea previously expressed that the course of senescence may be limited by a chemical process.

Some indices of senescence, such as the declining ability of the eye to accommodate itself to near objects (*cf.* Figure 29), do not follow the relationship represented by equation (1). This apparent exception may be due to insufficient data.

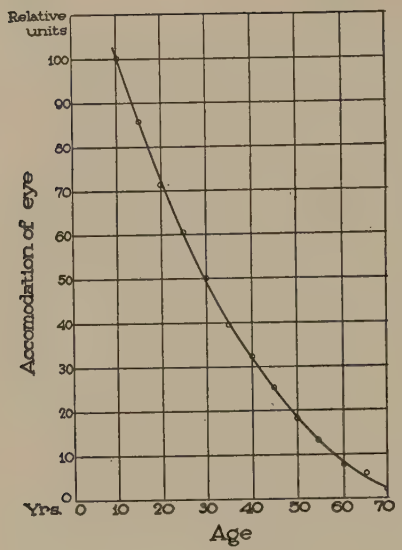


Figure 29. The course of senescence in man as measured by the decline in the range of accommodation of the eye with age expressed in terms of the accommodation of the eye at ten years as a base of 100 per cent. (Based on data given in Howell's *Textbook of Physiology*.)

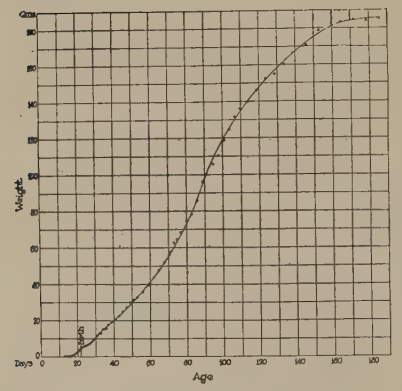


Figure 30. Growth curve of the albino rat.

IV. The Curve Representing the Course of Growth and Its Equation

1. *The general course of growth.*—Having obtained some idea relating to the course of senescence, we now proceed to a consideration of the course of growth. We shall first attempt to get a view of the growth curve as a whole, then we shall proceed to examine each of the two principal segments of which the growth curve seems to be made up.

The curve of growth in weight of the rat (Figure 30) is shown as a typical example of growth curves of animals that we have examined. The white rat is chosen for the typical illustration because, due to the labors of Dr. Henry H. Donaldson, more is known concerning the course of growth of the rat than that of any other animal, and because the rat is the first animal which was carefully studied from this viewpoint.

An inspection of Figure 30, representing the curve of growth in weight of the white

rat, gives us the impression that it bears some resemblance to a letter S, with the difference that the bend or inflection in the curve is not in the middle. The bend occurs, not in the center of the curve, as in the case with the letter S, but about one-third of the distance from the base line to the top of the curve. Different species of animals differ with regard to the position of this bend in the curve, as we shall presently show by means of graphs, but the general shape of the curve is the same in all animals.

Up to the point of inflection in the growth curves, the time rate of growth increases with the increase in size of the animal and we shall for this reason term this phase of growth, the *self-accelerating* phase. After the point of inflection, the time rate of growth decreases with the increase in size of the organisms, and we shall, therefore, call the phase of growth following the point of inflection the *self-inhibiting* phase of growth. We may note incidentally that we have examined a large number of growth curves of man, animals, and plants and found that the junction between the self-accelerating and the self-inhibiting phases of growth occurs, apparently without exception, at the time of puberty in animals, and at the time of flowering in plants.

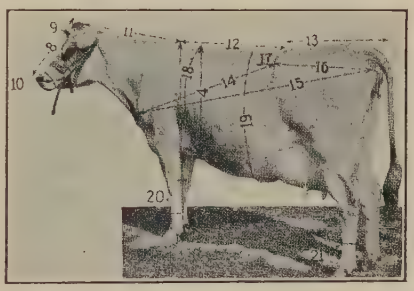


Figure 31. Skeletal measurements taken of dairy cattle. The measurements are referred to in the following charts by the numerals indicated on the photograph.

2. *The course of growth during the self-inhibiting phase of growth.*—(a) *Linear growth.*—Linear growth, that is, growth as measured by means of a measuring rod as, for example, growth in length of the body, presents a simpler type of growth curve than growth as measured by increasing weight. We shall, therefore, first consider curves of linear growth.

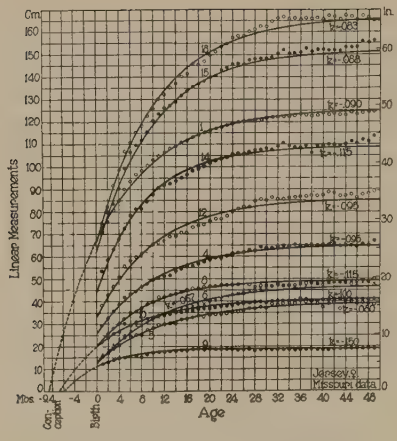


Figure 32. Growth in linear dimensions of Jersey cattle. The smooth curves passing through the observed values represent equation (2). The numerals refer to the measurements as indicated in Figure 31, as follows: 18 heart girth, 15 from point of shoulder to ischium, 1 height at withers, 14 from point of shoulder to a point of hips, 12 from highest point of withers to a line between hips, 4 depth of chest just behind elbow joint, 8 length from poll to point of muzzle, 6 width of hips, 10 circumference of muzzle at opening of mouth, 5 width of chest just behind the elbow joint, and 9 width of forehead. *k* represents the fractional decline in growth in successive months.

Figure 31 shows some of the linear measurements that were taken on dairy cattle in the Dairy Department of the University of Missouri, and Figure 32 shows typical growth curves thus obtained. The smooth curves passing through the circles, etc., were plotted according to the formula

$$W = A - Be^{-kt} \qquad (2)$$

in which W represents the value of the linear measurement, or weight, at the age t. A is the value of linear measurement, or weight, at maturity and e is the natural base of logarithms. *k* is the fractional decline in the monthly gains. Thus, if the gain in a certain measurement is 100 units during one month, and 90 units during the following month, then clearly the fractional decline per month is $\frac{10}{100}$ or 0.1 or 10 per cent. The agreement between observed values and the curve computed from this formula is evidently satisfactory.

The agreement between the circles, which represent the observed values, and the smooth curves which were derived from the formula, indicates that the fundamental characteristic of linear growth in dairy cattle is that the gains or increments per unit time decline at a constant ratio, or relative rate, represented by the value *k* in the formula, and the formula is thus an elegant descriptive statement of the time relations of linear

growth. This formula, too, is one used to represent the course of change of certain chemical reactions, which is in harmony with our tentative generalization or law that the course of growth may be limited by a physico-chemical reaction.

(b) *Growth in weight.*—While the formula (2) can be used to represent nearly the whole of the extra-uterine period of linear growth in cattle, it can be used to represent growth in

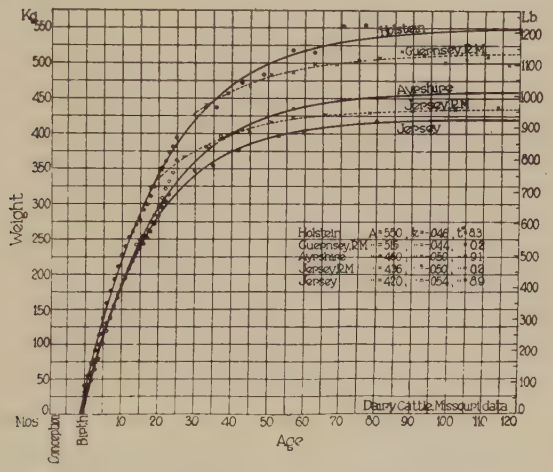


Figure 33. Growth in weight of the dairy cow. The circles are observed values, the smooth curve was drawn from the equation given on the chart. The agreement between circles and curve is excellent after the point of inflection, which is about five months after birth.

weight in this species only following the age of about five months after birth. Figure 33 illustrates this statement. The circles represent observed values; the smooth curve was plotted according to the equation shown in the chart. Satisfactory agreement between observed and computed values does not begin until about fifteen months after conception (*i.e.*, three to six months after birth). When the theoretical curve is extrapolated it meets the age axis not at zero, but at 8.9 months.

What was said respecting the agreement between observed and computed values for the cow is also true for all other ani-

mals examined; and not only for growth in weight, but also for growth in many physiological functions as, for example, growth in milk secretion shown in Figure 24.

The mathematically-minded reader may be interested to know that equation (2) is the integral form of the equation

$$\frac{dW}{dt} = k(A - W) \qquad (3)$$

in which $\frac{dW}{dt}$ is the instantaneous velocity of growth. The other symbols have the same meaning as in equation (2). According to equation (3), the velocity of growth is not dependent on age, but on the growth remaining to be made to reach the mature weight A. Data on delayed growth obtained by Osborne and Mendel (*cf.* Figure 34) indicate that within certain limits the velocity of growth is, indeed, independent of age.

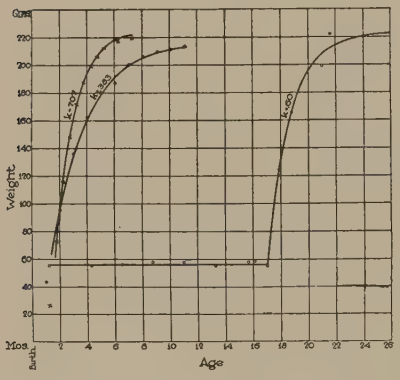


Figure 34. Growth as a function of the mature weight, and not of age. One of the curves on the left ($k = .383$) represents the course of growth of Dr. King's 16-25 generations inbred series of female rats. The other curve on the left ($k = .707$) represents the course of growth of the female rats of Sherman and McLeod. The curve on the right was plotted from data of female rat 2033 of Osborne and Mendel. By means of a decreased food supply, this rat was kept at a constant body weight of 55 grams from the age of 1.3 months (corresponding to about 3 to 4 years in man), to the age of 17.1 months (corresponding to about 43 years in man). When an adequate food supply became accessible, the rat began to grow at a rate characteristic of its weight and not of its age, thus indicating that, within certain limits, growth is independent of age. k is a measure of the steepness of the curve, that is, of the rapidity with which the mature weight is reached. It is evident that the slope of the experimental rat of Osborne and Mendel is of the same order as of the normal rats.

3. *The course of growth during the self-accelerating phase of growth. Growth cycles versus metamorphosis.*— We have found that the course of growth of the self-inhibiting phase of growth is relatively simple: The time rate of growth declines at a constant percentage rate as indicated by equations (2) and (3). The situation is somewhat more complex as it relates to

the self-accelerating phase of growth (the phase preceding puberty in animals and flowering in plants).

Robertson was probably the first to attempt a rational quantitative analysis of the growth curve, including the self-accelerating phase of growth. Space does not permit to give a detailed exposition of Robertson's work on growth and of the critical literature that it has brought forth. I shall, therefore, take the liberty of explaining the situation as I see it in as brief a manner as I can, referring the reader for details to Robertson's monograph on *The Chemical Basis of Growth and Senescence*, and to a paper in the *J. Gen. Physiol.*, 1926, VIII, 463; also to two papers by Davenport, one on "Human Metamorphosis" in *Am. J. Physical Anthropology*, 1926, IX, 205, and another on "The Human Growth Curve" in *J. Gen. Physiol.*, 1926, X, 205.

It is well known that certain kinds of animals (for example, insects and amphibians) pass through several distinct stages of growth separated from each other by changes known as metamorphoses. Everyone has heard, for example, of the metamorphosis of a maggot into a fly or of a tadpole into a frog. It is legitimate to ask the question whether warm-blooded animals likewise pass through stages of growth more or less distinct, analogous to metamorphosis in cold-blooded animals. In 1908 Robertson published a paper in which he showed that warm-blooded animals do, in fact, pass through several stages of growth, which he termed *growth cycles*. He analyzed these cycles mathematically from the point of view of the physical chemist, and he came to the conclusion that each of these cycles is limited by an autocatalytic mono-

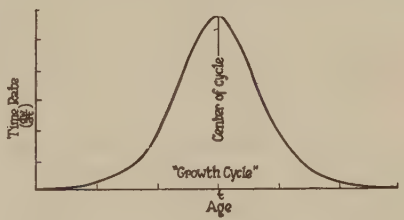


Figure 35. The theoretical curve of Robertson's cycle. The axis of ordinates represents time rates of growth, that is, gains in weight per unit time. The axis of abscissae represents ages. According to Robertson, there are at least three cycles (infantile, juvenile, and adolescent), of similar shape in the time rate curves of higher animals. Each cycle is, according to Robertson, (theoretically) symmetrical about its center.

molecular reaction. According to Robertson, there are at least three such cycles in higher animals and in man, namely, the infantile, juvenile, and adolescent cycles. According to Robertson's theory, each of these cycles, if not complicated by other cycles, is symmetrical about its center as shown in Figure 35. This conception of Robertson's brought forth a large critical literature, the latest of which at the time this book goes to press, is the one by Davenport on "Human Metamorphosis," also the one on the "Human Growth Curve."

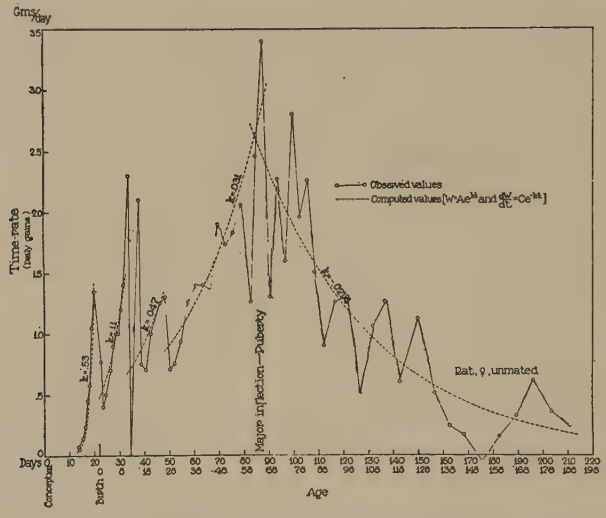


Figure 36. The change in speed (*i.e.*, in time rate or velocity) of growth of the white rat with advancing age. The circles represent values observed by Donaldson, Dunn, and Watson.

Figure 36 shows time rates of growth (gains in weight per day) plotted against age for the white rat. The circles represent observed values. Now it is possible, by a process of smoothing, to obtain an effect of three, or even four "cycles." As far as fitting Robertson's equation to the cycles is concerned, it can be fitted quite satisfactorily to the adolescent cycle with a maximum gain at about sixty days of age. But the fitting of Robertson's equation is much more difficult of accomplishment, if at

all possible, for the infantile and the juvenile cycles. This naturally leaves room for differences of opinion regarding the reality of the Robertsonian cycles.

To throw further light on this question, we have plotted the weights of the rats represented in Figure 36 on arithlog paper.

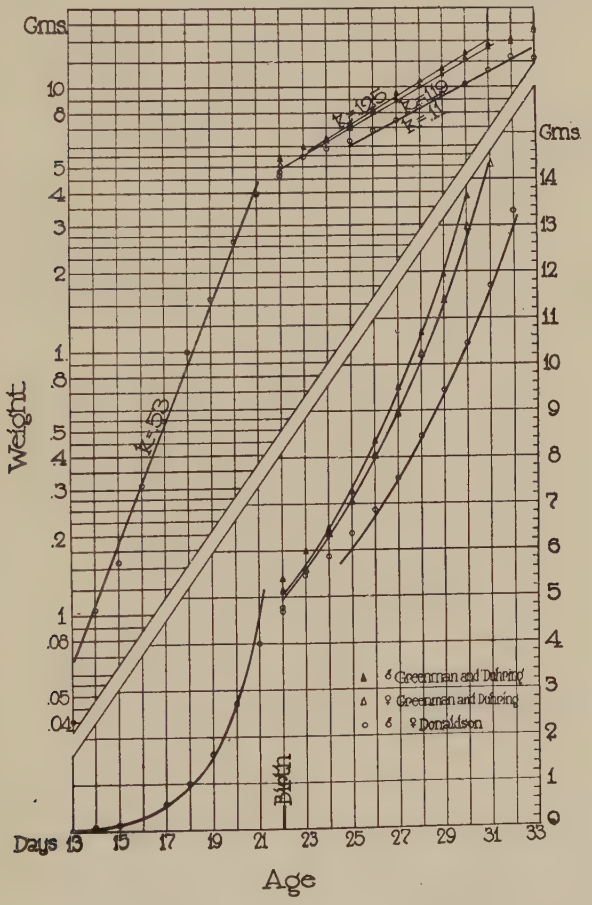


Figure 37. Growth data of the rat plotted on arithlog paper. The data points are distributed about a straight line from 13 days after conception until birth. The slope of the line indicates that growth during this period takes place at 53 per cent per day. At birth, there is a sudden break, a "metamorphosis," and a drop to a lower but (approximately) constant percentage rate (of about 12 per cent per day).

As previously explained, when data plotted on arithlog paper are distributed about a straight line, it may be concluded that the percentage rate of growth is constant. Now the arithlog charts representing data from thirteen days after conception (that is nine days preceding birth) up to ninety-five days after

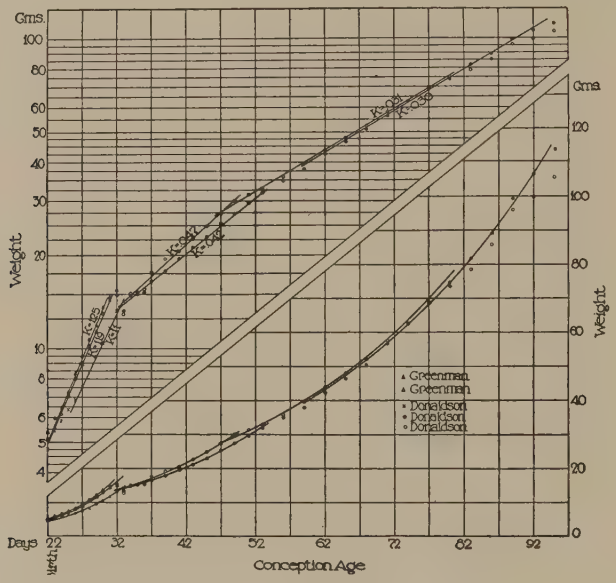


Figure 38. Growth data of the rat plotted on arithlog paper beginning with birth (about 22 days after conception). There appears to be a drop in the percentage rate of growth ten days after birth (about 5 per cent per day) and possibly another about one month after birth (about 3 per cent per day). Puberty occurs about 95 days after conception when the self-accelerating phase of growth is changed to the self-inhibiting phase of growth.

conception, shown in Figures 37 and 38, tell a somewhat different story from the one conceived by Robertson. These two charts say in effect that (1) up to puberty (about seventy days after birth or ninety days after conception in the white rat) the growth curve is made up of at least four segments, or, if one prefers, "cycles"; (2) the percentage rate of growth is constant during the periods represented by the segments or cycles;

and (3) there are relatively abrupt breaks between these cycles, the degree of abruptness being of the order of metamorphosis in cold-blooded animals.

The broken curves in Figure 36 were drawn in on the assumption that such phases of constant percentage rates of growth are present and that they are separated by breaks. In

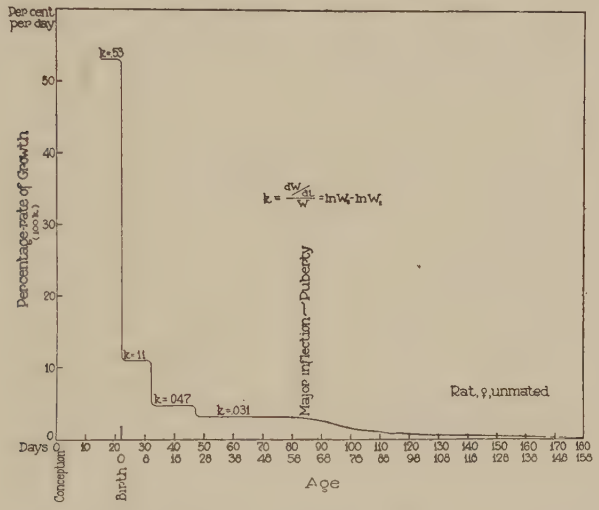


Figure 39. The value of k (relative rates of growth) plotted against age.

other words, the up-and-down fluctuations do not represent cycles of the kind shown in Figure 35, but rather successive segments of constant growth rate, separated from each other by relatively abrupt changes, which may be termed "metamorphoses."

If the percentage rates of growth (*i.e.*, 100k in Figures 36 and 39) are plotted against age, we obtain Figure 39, which exhibits the conception of "metamorphosis" in warm-blooded animals in quite a spectacular fashion.

According to Figures 37 and 39, the percentage rate of growth in the rat for the earliest period for which data are

available is only 53 per cent per day. This is a much lower value than one might infer from reading such works as the book entitled *The Problem of Age Growth and Death* (New York, 1908), by C. S. Minot.

By way of summary it may be said that the self-accelerating phase of growth is made up of several segments. Each segment represents a period of growth at constant percentage rate which may be represented by the equation

$$W = Ae^{kt} \qquad (4)$$

in which W is the weight of the animal at the age t, e is the base of natural logarithms, and k is the relative (or when multiplied by 100 the percentage) rate of growth. The segments of constant growth rate are separated by relatively abrupt breaks, the abruptness of the breaks being of the order of metamorphosis in cold-blooded animals.

V. A Set of Physico-Chemical Postulates on the Dynamics and Kinetics of Growth

Having considered the detailed features of the growth curve there remains the desire to contemplate the process of growth as a whole, and to formulate the results in a series of postulates or propositions. These propositions cannot be demonstrated, but they seem to be reasonable.

1. Why does growth occur? Because there is an inherent tendency, or force, which causes cells to divide. The detailed mechanism of this force is not clear; no more clear, for example, than the mechanism concerned in the force of gravitation which causes a pendulum to vibrate.

2. Why does growth cease? Because of the finite nature of the universe in which the reproducing cells find themselves. Growth is inhibited by the products of growth, the concentrations of which on account of the finite nature of the universe increase with age. Thus bacteria which turn milk sugar into lactic acid, thereby souring the milk, sooner or later cease grow-

ing because of the inhibiting effect of the lactic acid, or ultimately, because of the finite nature of the milk container (which is the universe for these bacteria). If the receptacle holding the milk were indefinitely large the concentration of the acid would always be insignificant, and the bacteria could go on growing at a constant percentage rate indefinitely. The same general reasoning probably applies to the limited period of growth in the tissue in the living chicken as contrasted to the indefinite period of growth of the same tissue when grown *in vitro* by the method of continued irrigation developed by Carrel and associates.

3. Why should the body grow at a constant percentage rate in the earlier periods of its life history? Because of the tendency of cells to reproduce at a constant percentage rate, that is, at equal intervals of time, when all other conditions remain the same.

4. Why should there be breaks in the growth curves of higher animals corresponding to metamorphosis in lower animals (*cf.* Figures 37 and 39)? Because certain growth-inhibiting influences exceed certain threshold values. Thus the milk-souring organisms, B. *lactis acidi*, grow at a constant percentage rate until the acidity designated by pH 4.7 is reached; pH 4.7 is, therefore, the threshold value for this type of organism in milk. In multicellular animals the nature of the threshold mechanisms is less understood, but mechanisms of the nature of hormonic action may be concerned in the process. Thus there is a species of salamander in Mexico which does not normally metamorphose. Recently specimens of this salamander were fed with thyroid substance and thus brought about metamorphosis. According to Gudernatsch, metamorphoses in certain tadpoles which normally occur during the third or fourth month of life can be brought about at will almost at any age by feeding thyroid substance.

5. Following puberty, the percentage rate of growth declines constantly. All the buffer mechanisms neutralizing the effects

of the growth-inhibiting substances have been used up on reaching this stage, and the process is necessarily approaching a standstill, or, to use a physico-chemical term, growth is approaching a state of equilibrium.

Indeed, the situation is exactly as that taking place in a physico-chemical system undergoing a so-called autocatalytic reaction. Thus Figure 40 indicating the course of oxidation of linseed oil is an example of an autocatalytic reaction, and it is very similar in general shape to the Figure 30, the growth curve of the rat. The work of Bray suggests the possibility that curves of inorganic chemical reaction *in vitro* are not as uneventful as might be inferred from Figure 40, but on the contrary they are pulsating in nature and probably pass through fluctuations in velocity comparable to the fluctuations indicated by the growth curves in Figure 36.

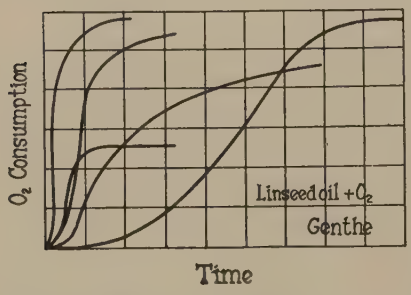


Figure 40. Time curves of oxidation of linseed oil under various conditions (after Genthe).

The general explanation for the shape of the time curve of chemical reactions is applicable for explaining the shape of the age curve of growth. In both cases the time curves of transformation are shaped, first, by the tendency of the reacting substances (substrates) to give rise to the products of the reaction; second, by the "back pressure" of the products of the reaction, caused by the finite nature of the "universe," inhibiting the speed of transformation; and, third, the effect of catalysts on the speed of transformation.

These general mechanisms appear to hold true, not only for growth of individuals, but also for the growth of populations. Indeed, we are concerned with populations in all cases. In chemical reactions we are concerned with populations of molecules; in growth of multicellular organisms, we are concerned

with populations of cells. The general course of growth of populations and of multicellular organisms must therefore be the same. As a matter of fact, it is quite a simple matter to make the curves of animals, plants, and populations to coincide, at least with respect to the self-inhibiting phase of growth as shown in Figure 41.

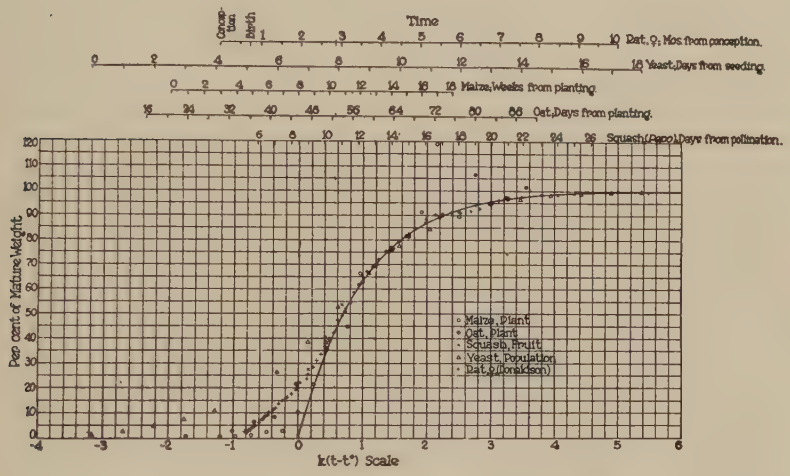


Figure 41. The growth curves of a multicellular animal (rat), population (yeast cells), plant (maize and oat), and fruit (squash) were made to coincide with respect to the self-inhibiting phase of growth.

Of course, there are differences in details of the curves, as shown, for example, in Figure 42 in which different species of animals and man were plotted, but the general similarity between the curves is evident.

Figure 42 may be of special interest to students of evolution and of education on account of the fact that it shows in a most striking manner the extremely long juvenile period in man. Other species go through a juvenile period corresponding to that in man, but the length of this period in animals is relatively insignificant when compared to that of man. It may be noted incidentally that one of the unique characteristics of the human

family, the simultaneous presence of several dependent children of different ages, is based on this fact. With the beginning of puberty, however, the difference between man and animals, as far as the shape of the curve is concerned, disappears.

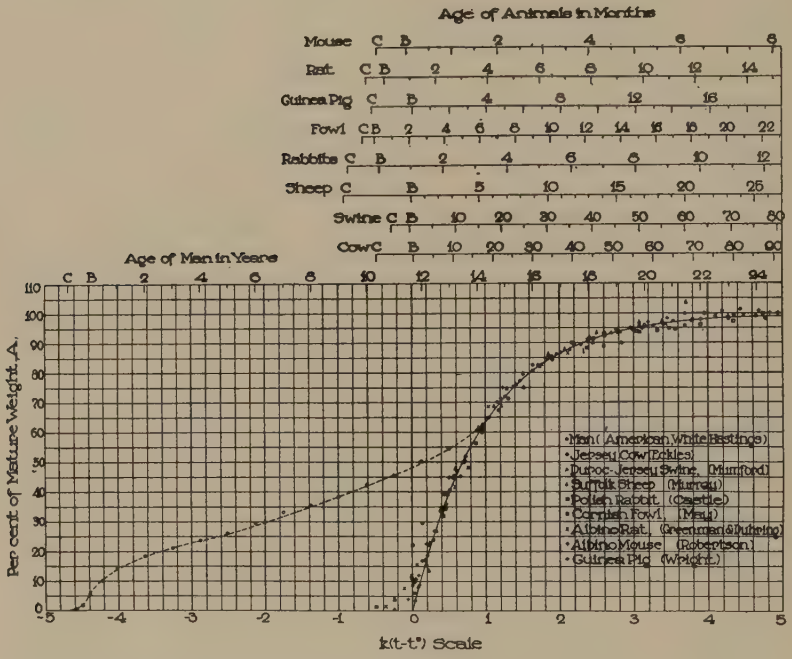


Figure 42. An equivalence chart of man and animals. The curve of man is conspicuous for its extraordinarily long juvenile period.

VI. Death

It is hardly possible to discuss growth and senescence without at the same time thinking of death, for death is the natural concomitant of growth and senescence. Someone has said, with much truth, that we begin to die the moment we are born.

The various theories of death have been recently summarized and discussed with much insight by Raymond Pearl in his monograph on the *Biology of Death*, and we need not therefore

stop to discuss this problem. We shall only express the general theory of this phenomenon and substantiate this theory by means of a curve (Figure 43).

It was pointed out in the introductory section that growth in higher animals is due primarily to the increasing number of cells; also, that the successive increases in the number of cells decline with age due to some unfavorable physico-chemical influence, or changes in its "universe," or in the medium surrounding the cells. (It is on the basis of the assumption that such a physico-chemical change takes place that we have employed the equation of physico-chemical reactions to represent the course of growth.) As the division-rate of the cells decreases with age, the cells probably undergo some change in their colloid structure. This change probably constitutes senescence, and death is due to the breakdown of some essential organ whose cells, weakened by the process of senescence, give way under a given set of unfavorable conditions.

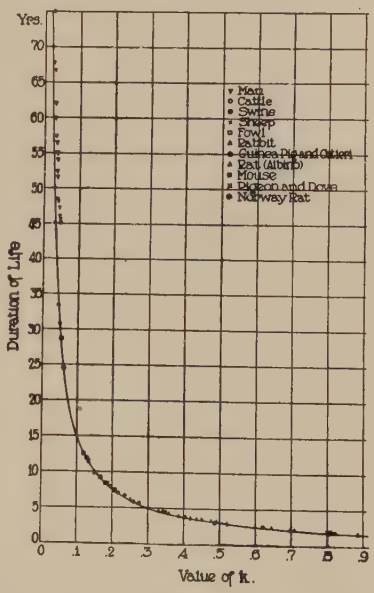


Figure 43. The relation between the rapidity with which the mature weight is reached, k of equation (2), and duration of life. The smooth curve was drawn on the assumptions that (1) the duration of life is inversely proportional to the value of k, that is, it is roughly proportional to the time required to reach maturity, and (2) that the duration of life of Donaldson's female rat is three years.

Now, if there is a relation between the decline in the division rate of cells with age (*i.e.*, the decline in the speed of growth with age) and duration of life as explained above, then the average duration of life of a species of animals should be (all other conditions being the same) inversely proportional to the decline in the velocity of growth with age. As a matter of fact,

this seems to be the case, as is shown in Figure 43, in which the duration of life is plotted against k, the fractional decline in the velocity of growth with advancing age.

Chapter III

Some Relations Between Growth and Nutrition

By Albert G. Hogan

Professor of Agricultural Chemistry, University of Missouri

SOME RELATIONS BETWEEN GROWTH AND NUTRITION

IT is unnecessary to point out that growth is one of the most important and fundamental phenomena with which we have to deal. Numerous problems suggest themselves in this connection, and they may be approached from diverse viewpoints each of peculiar interest. We may say at once that the possibilities of growth, and the capacity to grow, are determined by heredity, and are strictly limited. We are convinced, therefore, that we may attain a certain size, but that size is determined by heredity and there is no possibility of ever exceeding a certain maximum. There are giants in the world, but no one knows the secret of producing giants at will. We assume, then, that there is a more or less definite point beyond which growth may not proceed; so we should stress the fact that this maximum (or optimum possibility) may not be attained, due to some limitation of the environment. It is with one phase of the environment that we are now chiefly concerned, and that is the food supply, its composition, and amount.

I. The Nutrients Now Recognized as Such

At this time we shall only concern ourselves generally with the substances that are considered as nutrients for the animal body, and specifically with the following: proteins, fats, carbohydrates, minerals, and vitamins.

We have purposely left out some substances that might properly be included, such as oxygen and water, and there may be others as yet unrecognized. So we will add "etc." in order to be sure that nothing is omitted. After this brief introduction, we shall proceed to a discussion of these groups of compounds individually, and to some extent collectively, with regard to their rôles in nutrition, and shall begin with the proteins.

The Proteins. Special importance has long been attached to protein because of the predominating rôle it plays, not only in the structure of the cell, and of the body, but also in the various physiological processes.

It has been recognized for years that different proteins have unequal values as regards their more important physiological rôle, but the explanation of this fact was deferred until some knowledge was gained as to the constitution of the protein molecule. After it was once established that this class of compounds yields amino acids on hydrolysis, the way became clear to a better understanding of the limiting factors as regards the biological value of proteins.

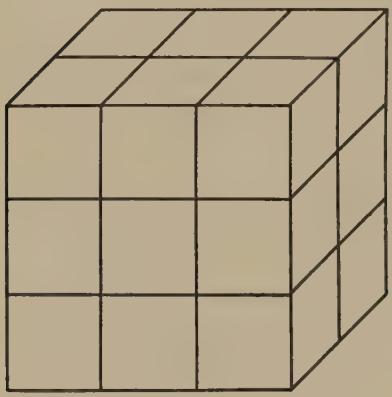


Figure 44. A diagram drawn to illustrate the fact that on hydrolysis the protein molecule yields amino acids. The large figure represents the protein molecule, the smaller ones the molecules of the amino acids that compose it.

The structure of the protein molecule may be illustrated in a diagrammatic, and rather crude, manner that will be sufficiently accurate for our purpose. Suppose we take the smallest possible sample of a protein that it is theoretically possible to take without changing its percentage composition. We will call this sample a protein molecule, and though it would be much too small to see, even with the most powerful microscope, there is little doubt that this molecule occupies a fairly constant volume and has a definite geometrical pattern. Our information on these points is very slight at best, so at the present time we are unable to describe them with any degree of accuracy. We feel very certain, however, that if we could enlarge our molecule sufficiently, and see its component parts, we would see that the protein molecule is formed by the union of many smaller molecules, such as

glycocoll (the simplest), glutaminic acid, lysine, arginine, histidine, tryptophane, tyrosine, and cystine. In addition to these ten or more other cleavage products have been identified.

It soon became evident that proteins may yield the same amino acids but yield them in quite different proportions. For example, gliadin, present in wheat, contains about one per cent lysine, and casein contains approximately 7.5 per cent. Lactalbumin contains about 9 per cent glutaminic acid, gliadin, about 44 per cent. It is also known that certain amino acids are entirely absent from some proteins. Thus, glycocoll has never been identified in the hydrolytic products of gliadin, zein, casein, or lactalbumin.

We have then taken it for granted that there are different kinds of proteins, and it has been demonstrated that there are indeed many different ones. Reference to our diagram should make that clear. Evidently a change in the arrangement of the individual amino acids would make theoretically possible an almost limitless number of different geometrical patterns, and so of different proteins.

If the complexity is further increased by changing the proportions in which the amino acids exist, then there is for all practical purposes no limit to the number of these compounds. Thus the tissues of one animal are in some degree unlike those of every other animal. Furthermore, the various tissues of one animal contain many different kinds of proteins. We also know that the nutritional value of different proteins varies. In general we say that animal proteins have a high biological value and plant proteins have a low biological value. Numerous demonstrations of this fact have been described, but we will content ourselves with one.

It is a commonplace among feeders of live stock that corn alone is a very poor diet for growing animals. From a nutritional standpoint this cereal, and others too, for that matter, are inadequate as a complete diet in at least two respects; one of these is the protein factor. Our textbooks commonly state that

cereals are low in protein, and that is true. The proteins themselves, however, are also of poor quality. The example we have chosen is adapted from data published[1] a few years ago on the nutritional requirements of swine.

Table I

THE BIOLOGICAL VALUE OF THE PROTEINS OF CORN AS COMPARED WITH CASEIN

Lot no.		31	34	36	35
Nutritive ratio		1:8.8	1:8.8	1:6	1:3
Ration	Corn	97.5	25.00	50.00	50.00
	Casein		3.00	2.82	11.68
	Starch		21.40		
	Salt mixture	2.5	1.24	1.32	1.54
		Per cent	*Per cent*	*Per cent*	*Per cent*
Protein	Corn	10.88	5.64	10.29	8.77
	Supplement		4.87	4.21	14.91
Ether extract		4.58	3.02	4.97	5.92
N-Free extract		80.30	82.80	76.15	65.80
Ash		4.27	3.73	4.33	4.51
		Lbs.	*Lbs.*	*Lbs.*	*Lbs.*
Avg. initial wt. 7-3-'15		25.3	24.0	20.3	19.7
Avg. final wt. 12-30-'15		37.6	164.7	200.0	200.7
Gain		12.3	140.7	179.7	181.0
Total dry matter consumed		114.6	433.6	513.2	530.2

You will note that the ration of corn alone barely sufficed for maintenance. The ration of the second group was approximately the same as that of the first, if we suppose that about one-half of the corn protein had been replaced by casein. The gains made by this group were not rapid, but the total weight gained was about twenty times more than that of the first group. This chart also brings out another point—the supplementing value of unbalanced proteins. We may say from previous experience that if the only protein in this diet had been 4.78 per cent casein, there would have been no gain. It is obvious that 5.64 per cent of corn protein is ineffective, but the combination of the two is far

superior to either alone. We explain that fact by saying each protein supplements the other.

Since proteins differ so enormously in their nutritional or biological value, efforts were initiated years ago to discover the reason; and since these substances differ, not only quantitatively in the amino acids they yield, but also qualitatively in those that are present, interest was directed at once to the possibility that some of these amino acids may be indispensable, while others are not required at all by the animal body.

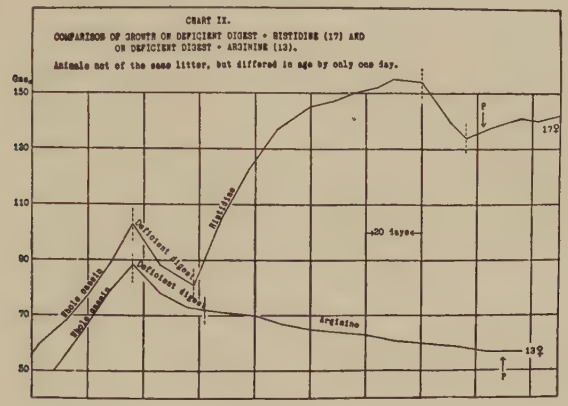


Figure 45. Histidine is an essential amino acid. After Rose and Cox. By permission of the *Journal of Biological Chemistry.*

One of the earliest methods of attacking this problem was that of hydrolyzing the proteins, either by enzymes or by acids, and then feeding the product. Variations of this method were to separate certain amino acids from the mixture and then feed the remainder. Space will not permit more than mere mention of workers in this field, but apparently Henriques and Hansen, over forty years ago, were pioneers. These earlier methods were extended somewhat by other workers, and the net result of their work would seem to show that tryptophane is indispensable, but tyrosine is still questionable in that respect.

The most recent study of this nature is one reported by Rose and Cox.[2] They used rats as experimental animals, and supplied them with more or less conventional "synthetic" diets. The nitrogenous material was supplied in three forms: first, pure casein; second, casein that had been completely hydrolyzed; third, hydrolyzed casein from which the amino acids, arginine and histidine, had been removed. We will only say in regard to this report that the animals receiving casein grew rapidly, and

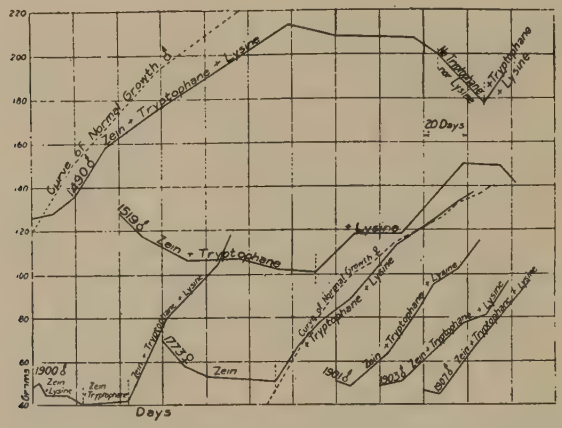


Figure 46. Zein lacks two essential amino acids, tryptophane and lysine. After Osborne and Mendel. By permission of the *Journal of Biological Chemistry.*

those on hydrolyzed casein from which arginine and histidine had been removed did not grow at all. The addition of arginine did not improve the diet, but the addition of histidine enabled the amino acid mixture to support growth. We may then provisionally place histidine in our list of essential amino acids.

This problem has been attacked in a slightly different manner by the use of proteins known to be deficient, and this method has probably been somewhat more fruitful up to date.

Striking evidence as to the indispensability of tryptophane has been published by Osborne and Mendel.[3] Rations containing

zein (prepared from maize) as the sole protein did not suffice even for maintenance. If such a ration were supplemented with tryptophane, maintenance could be secured for at least some time. No other amino acid can take the place of tryptophane. When the ration was supplemented with lysine and tryptophane, growth followed at nearly the normal rate. Since zein does not contain glycocoll these observations also yield evidence that glycocoll is dispensable as a dietary component. The same paper also contains additional evidence that lysine is indispensable for growth. Rats were fed a ration in which the protein was supplied as gliadin, and they noted that the gliadin rations permitted maintenance, but no growth. If, however, lysine (3 per cent of the protein) were added to the ration, normal growth resulted. If the lysine were subsequently withdrawn, growth promptly ceased.

As to the indispensability of lysine for maintenance, it has not been possible to obtain unequivocal evidence from the use of gliadin, for it contains a small quantity of lysine. The author has reported[4] data which seem to afford direct evidence that lysine is also indispensable for maintenance. Rations which contained kafirin as the sole source of protein were fed to rats, but on such rations the animals slowly and continuously lost weight. Similar rations supplemented with lysine, however, permitted a slow rate of growth.

Osborne and Mendel have also shown[5] that though casein contains cystine, it contains it in less than the optimum quantity. Rats grew normally on diets containing 18 to 15 per cent of casein, but at less than the normal rate when the diet contained only 12 per cent of this protein. When the diet contained 9 per cent, growth was checked sharply. Evidently in rations of the character used the minimum quantity of protein on which normal growth may be secured lies somewhere between 12 and 15 per cent. If, however, cystine were added to these diets, normal growth could be attained at considerably lower levels.

The Fats. When we mention the word nutrients, we at once

think of protein, fat, and carbohydrate. Although each group is unquestionably a desirable nutrient, it is quite another matter to say that each is a *necessary* nutrient, and so we may well ask whether or not any of them may be dispensable.

We may say at once that proteins are obviously indispensable. The necessity of fat in the diet is, however, much less certain. In the first place, the technical difficulties in planning a ration satisfactorily meeting the requirements of such a test are not inconsiderable. The ration must not only be free from fat,

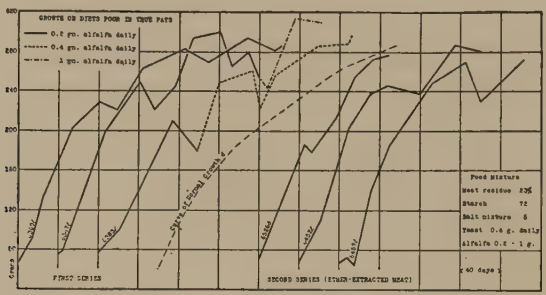


Figure 47. Growth on diets almost entirely free from preformed fat. After Osborne and Mendel. Courtesy of the National Academy of Sciences.

but in addition must include all other substances known to be essential. That class of vitamins commonly called fat-soluble must obviously be included. In view of these considerations, some of the earlier reports on this topic must be regarded with caution.

The best available evidence on this point has been supplied by Osborne and Mendel.[6]

In one series the ration was:

Meat residue	23 per cent
Starch	72 per cent
Salt mixture	5 per cent

The vitamins were supplied in tablets, each one containing 0.4 gram yeast, 0.2 gram alfalfa, and 0.2 gram cane sugar,

each rat receiving one daily apart from the rest of the food. Such a ration contained at most an exceedingly small quantity of fat, but yet permitted the rats to attain normal mature weights.

Needless to say, these views as to the non-necessity of fat in the diet do not indicate that it is also undesirable. Fats are a valuable source of energy, and are useful reagents in the hands of a skilful cook.

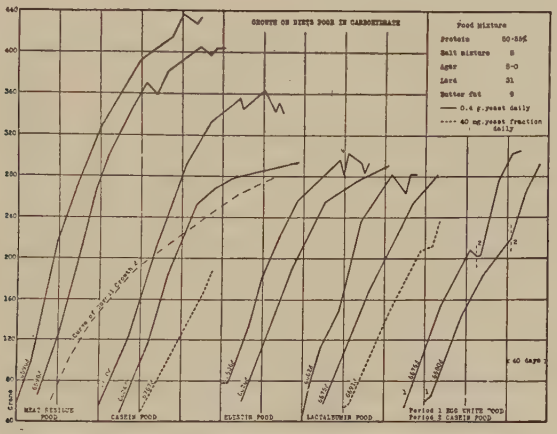


Figure 48. Growth on diets almost entirely free from preformed carbohydrate. After Osborne and Mendel. Courtesy of the National Academy of Sciences.

The Carbohydrates. Since there is doubt as to the need of fat in the dietary, we may also raise the question, Is carbohydrate an essential constituent of the diet? Some theoretical considerations might lead us to believe that carbohydrate is an indispensable dietary component. According to generally current physiological teaching, fats burn in the flame of carbohydrates, and if the supply of available carbohydrate is deficient, fats will not be completely oxidized and so acidosis may result. It is, however, well known that carbohydrates may be derived from proteins in normal metabolism, so it is possible that preformed

carbohydrate need not necessarily be included in the diet. This question also was investigated experimentally by Osborne and Mendel and they found that the response of the rats was largely determined by the quantity of fat in the diet. One ration (meat residue 20 per cent, beef fat 61 per cent, butter fat 14 per cent, salt mixture 5 per cent, vitamin B tablets in addition) permitted a fairly rapid rate of growth to be maintained. A ration containing casein 15 per cent, and fat 80 per cent was, however, decidedly less satisfactory.

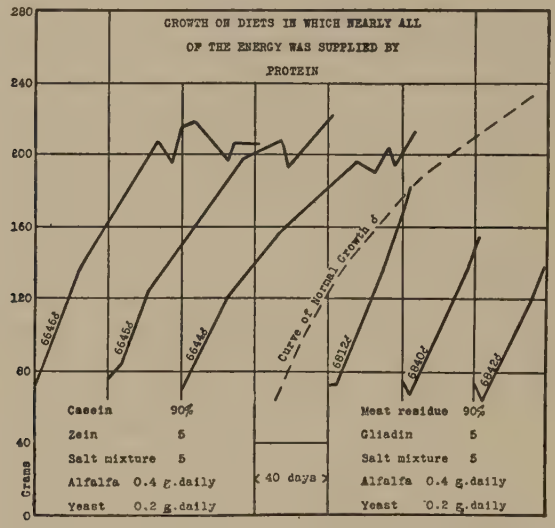


Figure 49. Growth on a diet practically free from both fats and carbohydrates.

In the last series to be described, the ration contained a very high percentage of protein and was practically devoid of both carbohydrate and fat. The ration consisted of meat residue 90 per cent, gliadin 5 per cent, salts 5 per cent, together with daily additions of yeast 200 mg., and alfalfa 400 mg. It will be observed from the chart that the animals grew rapidly, but the period of rapid growth was shortened, so the adult size was

somewhat subnormal. Some of the animals that had stopped growing at subnormal weights, again resumed growth when given a mixed diet, thus indicating that this high protein diet left something to be desired.

In connection with diets of a high protein content the question of damage to the kidney often arises. Newburgh[7] states that a high protein dietary is associated with renal disorders. Polvogt, McCollum, and Simmonds[8] state that the kidneys of rats suffer lesions from excessive protein feeding. Osborne and Mendel[9] report that though they fed protein at a higher level than did the Johns Hopkins group, their animals exhibited no lesions. The kidneys were, however, about one-third larger, and about twice as heavy as the kidneys of normal control rats. The view of Osborne and Mendel is supported by A. J. Miller.[10]

The Inorganic Nutrients. It has been recognized for years that certain mineral elements are indispensable components of the dietary, but knowledge of their specific functions is in most instances very limited. In general, therefore, it is our practice to speak of the "ash" content of foods when we consider their content of mineral matter, though it has become a custom to give separate consideration to calcium and phosphorus. The reason for that is, of course, obvious. Growing animals, and those secreting milk, have requirements for those elements representing quantities of fairly large magnitude, and the minimum quantities required are fairly well defined at present. In the case of the other elements, however, there is almost no good evidence as to the minimum requirement for growth or as to any specific rôle they play in that process.

Some of the feeds commonly employed are notably deficient in mineral elements and it was recognized in the early history of the science of nutrition that the cereals, notably maize, are deficient in both protein and mineral constituents. Some years ago the writer was associated for a time with an investigation in which swine were used for a study of the nutritional properties

of corn, and it was shown[10a] that, at least for swine, protein is the first limiting factor, and mineral constituents the second.

As to the individual mineral elements, it was well known from the first that, to a certain extent at least, these elements could be supplied in inorganic form. The question has been raised, however, as to the possibility of entirely supplying the requirement for these materials in the form of inorganic salts. Many investigators have supposed that at least a certain quantity of phosphorus must be supplied in organic combination. For that reason considerable attention has been given to the lecithins, nucleins, and phytates, as sources of phosphorus. Röhmann, for example, stated[11] many years ago that the animal organism does not have the power of synthesizing the organic phosphorus constituents of the body.

Several years ago the Wisconsin Station[12] attempted to solve this problem. They undertook a study of the ability of the animal organism, swine, to use inorganic phosphorus in forming new growth. In all, five groups of animals were used. Lot 1 received the basal ration composed of rice, wheat gluten, and washed bran. Lots 2 and 3 received the basal ration, with the addition of various quantities of calcium phosphate. The ration supplied Lot 4 was made up of rice, wheat gluten, and unwashed bran. A ration containing corn, oats, shorts, and oil meal was supplied the fifth lot, as an additional control.

At first all groups did about equally well, but in about three months the lot receiving the basal ration began to show signs of distress. There was soon pronounced weakness of the hind quarters, the animals were unable to stand, and at the same time there was a considerable loss in weight. One of these pigs was killed for examination. The most important abnormality noted concerned the appearance of the bones, which were spongy and loose in texture. The specific gravity was less than one, and the ash content, on a moisture-free basis, was only about 33 per cent, while the ash content of normal bones is about 54 per cent.

The other pigs were given a diet of milk and wheat middlings, and were soon restored to a normal condition.

The other groups all made fair gains, though there was one exception in each of the groups, 2 and 3. As would be expected, all the variations in phosphorus content were in the bones; there were none in the fleshy tissue. It is now the general opinion that inorganic phosphorus can meet all the requirements for that element. We may also say that, with one exception, it is unnecessary to supply any of the mineral elements in organic combination. This exception is sulphur, due to the fact that the animal organism is unable to synthesize the sulphur-containing amino acid, cystine.

Numerous investigations have been made concerning the effect of a deficiency of calcium on the rate of growth. It is quite certain that if the ration is sufficiently low in calcium, and if the animals are sufficiently immature when placed on the diet, growth will be inhibited. It is, however, quite remarkable to what an extent an animal will grow on a ration deficient in calcium, provided all other factors are satisfactorily adjusted.

For example Voit[13] reports that if rations low in calcium are fed, growth will be normal if the ration is otherwise adequate. According to this observer the chief effect of a ration low in calcium is to produce a condition resembling rickets. A somewhat similar observation was made many years later by Aron and Sebauer.[14] They fed one group of dogs on a ration high in calcium and another group on a ration considerably lower in this element. Although the group receiving the ration low in calcium developed marked symptoms resembling rickets, both grew at practically the same rate. It is also worthy of note that there was some interference in locomotion of these animals and there were other symptoms of general *malaise*. This sort of investigation has been continued by Eckles and collaborators.[15] They began with two Jersey heifers about six months of age, which had been reared on a normal diet. One of these was

placed on a low calcium ration, containing as a source of roughage, corn, corn silage or corn stover, and timothy hay. Corn and gluten meal were fed as concentrates. The ration to supply larger quantities of calcium contained alfalfa hay and a concentrate made up of a mixture of corn, wheat bran, and cottonseed meal. The heifer which received the liberal quantity of calcium remained normal in health and vitality and grew at the normal rate. The one receiving the ration deficient in calcium, however, did not fare quite so well. For the first thirteen months she seemed to be quite normal, but then became stiff in the joints and developed an abnormal gait. Finally her knees were partially bent and after lying down she found it very difficult to rise again. The ration was then changed and the heifer became nearly normal in condition within a month.

More recent data (unpublished) obtained at this station, with swine, emphasize the great capacity of animals to adjust themselves to unfavorable dietary conditions as exemplified by a ration deficient in calcium. Female pigs, aged about sixteen weeks, were placed on a diet as low in calcium as it is practically possible to prepare. Analyses indicated that the ration contained less than 0.05 per cent of that element. If the pigs had been placed on this ration at eight weeks of age, we feel quite certain that the trial would have ended in disaster. These animals grew very well, however, though two sows suffered broken legs, and on post-mortem examination were found to have exceedingly soft, spongy bones. The others farrowed the following spring, but none were able to rear their young. One litter was very weak at birth, presumably because of the poor state of nutrition of the mother.

The importance and physiological rôle of iron has been emphasized for years. One of the recent reports,[16] of observations made on a practical swine-breeding experiment, again emphasizes the importance of iron for growing animals. The sows were left on pasture until two weeks of farrowing time, after which they were confined to pens and fed a ration of fishmeal,

corn, and brewers' offal. For the first three or four weeks after farrowing, the pigs seemed normal, but after that time deaths became numerous and post-mortem examinations revealed a variety of pathological conditions. The blood was much lighter in color than is normal and the count of red corpuscles was reduced to about three million per cmm. It seemed probable that the trouble was due to the lack of iron in the ration, so this was supplied in the form of ferric oxide. As a result the younger pigs developed no symptoms of the disease, and many of the affected animals recovered. There was also an increase in the hemoglobin content of the blood.

In regard to the more obscure mineral elements the best data we have are those obtained by Osborne and Mendel.[17] Their work was made possible by the recent discovery of the vitamins, and so the use of synthetic diets, composed of comparatively pure nutrients relatively free from inorganic contamination, was followed. Complex salt mixtures were then prepared, each free from some one of the elements to be investigated. These elements were as follows: sodium, potassium, magnesium, chlorine, calcium, and phosphorus, singly and in combination. The appended charts bring out some very striking facts. It will be noted that the quantity of magnesium, chlorine, sodium, and potassium for normal growth is very small indeed. A diet containing 0.01 per cent of magnesium, 0.03 per cent of potassium, and less than 0.04 per cent of either sodium or chlorine permitted normal growth. The one exception noted was a simultaneous reduction of both sodium and potassium. When both were decreased at once, growth stopped. Later, sodium only was added without much improving the rate of growth. Potassium was then substituted for sodium, and growth was resumed at a rapid rate. These observations, of course, do not indicate that these elements are not required, merely that they are husbanded with extraordinary tenacity. The quantity of chlorine that must be fed is very small, but if the gastric juice, containing hydrochloric acid, is removed, the results are speedily disastrous.

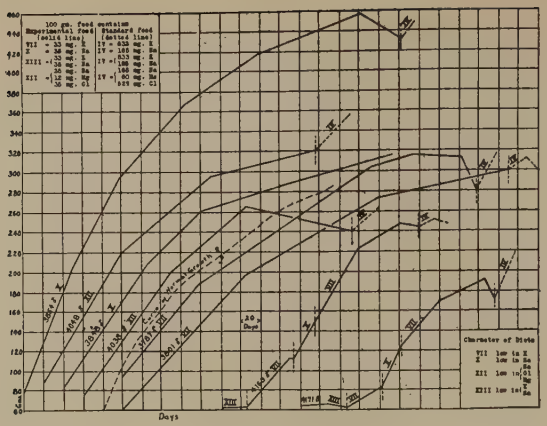


Figure 50.

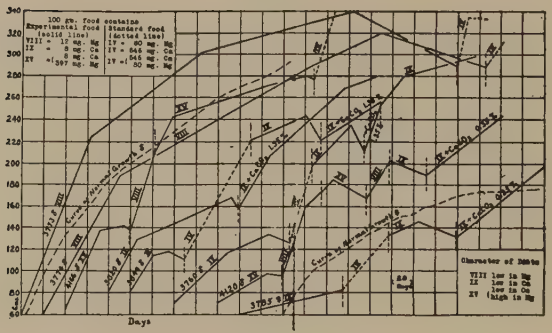


Figure 51.

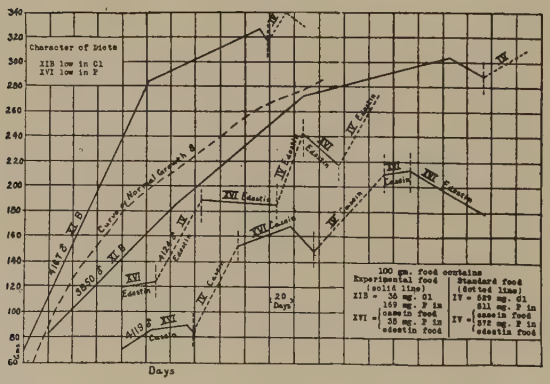


Figure 52.

Growing animals require only small quantities of any one of the following: Chlorine, sodium, potassium, or magnesium. The requirement for calcium or phosphorus is relatively much higher. After Osborne and Mendel. By permission of the *Journal of Biological Chemistry*.

Another element we should mention, iodin, is required only in minute quantities, yet it is known to be of the utmost importance. Many years ago Baumann[18] discovered iodin in the thyroid gland, and more recently the compound thyroxin in which it is present has been isolated by a young American chemist, Kendall.[19] It has been repeatedly and conclusively demonstrated that iodin, and thyroxin of the gland, play a determining rôle in growth and in normal metabolism. It is now possible to buy on the market iodized salt that may serve the same purpose. Practically all salt deposits contain iodin, but in our mania for consuming "pure" foods, we purify our salt until it is free of iodin, and then we put it back.

There is still some debate as to the dispensability of other elements, most of which are required only in minute traces, if required at all. Thus boron, silicon, manganese, arsenic, fluorine, zinc, and copper, have all been suggested as being indispensable. The difficulty in determining the facts is that even the most highly purified foods it is practicable to use in experimental work may contain a trace of the mineral in question.

The Vitamins. It seems strange that any nutritional factor as important as the vitamins could have eluded detection up to a time within the memory of us all. That these substances were not detected may be explained by the fact that they exist in such small quantities, and there is an enormous disproportion between their importance and the quantities that are necessary to insure nutritional well-being. It is easy to see now that ample evidence has existed for years to prove the existence of some unknown factor or factors in nutrition. This evidence did not become sufficiently conspicuous, however, to force itself upon our attention until comparatively recent years.

It is impossible to review the earlier history of the vitamin problem, but we may say that physiologists formerly believed that proteins, fats, carbohydrates, and salts were the only necessary constituents of an adequate diet. We would now say that, before the belief was justified, an experimental demonstration

should have been carried out to complete success. Such attempts, however, were not often made, and the few recorded were complete failures. One of the more significant of these was really an effort to solve another problem, the rôle of mineral salts in animal nutrition. Lunin[20] used mice as experimental animals, and attempted to maintain them on a diet of casein, butter, lactose, and the ash of milk. None of his animals, however, lived longer than a month on this ration, though they survived indefinitely on a diet of milk itself. Lunin himself expressly stated his belief that proteins, fats, carbohydrates, and salts are not capable of maintaining normal nutrition, and that milk must contain some other essential factor. His observations were recorded in Bunge's *Text Book of Physiological and Pathological Chemistry*, but they were not accorded the importance we now know they deserved.

It would seem desirable at this point to mention a disease that has in the past received considerable publicity, beriberi. In former years at least it was very prevalent in certain portions of the orient, Japan, the Philippine Islands, the Dutch East Indies, and other near-by regions. The symptoms are somewhat varied, but peripheral neuritis seems to be the most characteristic. For many years beriberi was regarded as a tropical disease, limited to rice-eating populations, but it is now known that the same symptoms will develop whenever the diet consists too exclusively of any highly milled cereal.

In 1897 a physician named Eijkman was attached as a medical officer to a prison in Java, where beriberi was common. Poultry, maintained by the institution, were largely fed table scraps, chiefly rice, and Eijkman[21] noted that they frequently exhibited symptoms very similar to those of his human patients. There is still some doubt that avian polyneuritis is entirely analogous to human beriberi, but such an analogy has been accepted by the great majority of physiologists. Beriberi was then subjected to intensive study, and though some of the observations were conflicting, it finally became established that the

polishing process, by which the germ and outer covering of the grain were removed, was largely responsible for the disease. Evidently the rice polishings contain something that is essential for normal nutrition, and this substance is absent from the portion we know as polished rice.

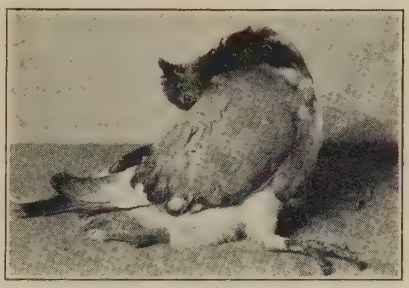


Figure 53. A typical case of avian polyneuritis, due to a lack of vitamin B.

Many ambitious efforts were made to isolate the active material from rice polishings, but though complete success has not been attained as yet, the results have been at least stimulating. We will not attempt any adequate description of these efforts, but mention the fact that, in 1911, Funk[22] obtained a few crystals of what he believed was the active curative agent, in the pure state. He stated that 4 mgm., roughly $\frac{1}{7000}$ of an ounce, were sufficient to cure a pigeon. It would seem now, however, that these crystals were not the pure curative agent, but that they carried the active agent as an impurity. Funk believed this substance, from a chemical standpoint, is an amine, and that it is of vital necessity. He called it, therefore, "vitamine," and the name has persisted, though we have no evidence that any of the unidentified factors are really amines.

Probably the next effort of this nature we should mention was that of Osborne and Mendel.[23] They used protein of a high degree of purity, and in addition starch, lard, salts, and sugar. It should be pointed out that their earlier efforts were unsuccessful, but they evidently believed the failures were due to some maladjustment of the salts. Accordingly they removed as completely as possible the proteins from skimmed milk, and so obtained, as they believed, essentially a mixture of milk sugar and milk salts. This mixture, "protein-free milk," was dried

and incorporated into their synthetic diets, and they then obtained at least a moderate degree of success. They observed, however, that in a few months young animals ceased growth and declined, so evidently the problem was not yet solved. Unfortunately, it will be necessary to pass over many important contributions, but we will take time to mention a publication of F. G. Hopkins.[24] He, too, used synthetic diets, and in some cases his experimental animals did fairly well. He remarked on the fact, however, that the successes were obtained when he employed relatively crude materials. It seemed that the more he purified the components the poorer were the results. Hopkins was convinced that his failures were due to the absence of some essential organic factor, and made it clear that the materials must have a high degree of potency, in very small amounts. Because of the small quantity necessary it seems that Hopkins believed the rôle of these accessory factors was that of a hormone or catalyst, and he suggested that they may serve as a stimulus to some of the organs of internal secretion. We may add that this rôle is just as obscure now as when postulated by Hopkins fourteen years ago.

We now enter on the period when a temporary solution of the problem was reached. In 1913 McCollum and Davis[25] reported that animals may be maintained for some time on a diet of casein, lactose, lard, and salts. If milk fat or egg fat were incorporated in the ration, however, fairly satisfactory growth followed. The month following the publication of McCollum and Davis' work, Osborne and Mendel[26] published a paper which confirmed it, in regard to the unique rôle of milk fat. Following these papers there was some confusion for two years as several workers were unable to repeat McCollum's work. However, in 1915, McCollum and Davis[27] demonstrated that two factors were concerned in the earlier failures. One is present in milk fat, as they had previously stated. The other was present in skim milk, and in yeast, as Funk had consistently maintained. It is obvious enough now that the earlier successes

as reported by McCollum and Davis, also by Osborne and Mendel, were due to unsuspected impurities. In the first case this impurity was present in the crude lactose employed, while in the latter it was present in the protein-free milk. Milk then contains both factors, and they may be roughly separated by removing the fat.

McCollum named these factors in the order in which they were first brought to his attention, not in the order in which they were really discovered, and the names were based on their solubility. Thus the vitamin in milk and egg fat was called Fat-Soluble A, and the other vitamin was called Water-Soluble B.

Figure 54. Avian xerophthalmia, due to a lack of vitamin A. Note that the eye is swollen and closed. Courtesy of Prof. H. L. Kempster.

Practically all workers in the field of nutrition have concurred that these two nutritional factors, A and B, do exist, though for some years there were at least a few dissenters. It was also tacitly assumed by the great majority that these two were the only unidentified factors, but gradually evidence was accumulated that made it certain that scurvy, also, is a deficiency disease. It has long been known that the disease is dietetic in origin, that it appears during periods when fresh foods are not available, and that it disappears when such materials are included in the diet.

Modern experimental work, however, had to await the discovery of an animal that is susceptible to scurvy, and that was afforded by the guinea pig. Apparently this was first noted by Professor Alex Holst,[28] University of Christiana, who made a careful study of guinea-pig scurvy. He showed that on a mixed vegetable diet, guinea pigs can be maintained in perfect health, but if all green feed is removed, so the animals must subsist on grain only, they develop the disease. He also demonstrated

that if these green foods are dried, or cooked for too long a time, they lose their antiscorbutic effect. Another important discovery[29] was made in Holst's laboratory, namely, that if the grains were germinated before being fed, they regained antiscorbutic potency. Since then the subject has been greatly expanded, and the antiscorbutic potency of practically all common foods has been determined.

The last of the so-called deficiency diseases to be mentioned is rickets, and it too has a long and distressing history. If we leap into the last few years, we may say it is now believed to be due to a disturbance in mineral metabolism. It is preponderatingly a disease of the growing organism, though it has its analogy in the adult also. The net result of the pathological condition is the failure of normal deposition of calcium salts in the bones. This is shown by the abnormally low content of salts in the bone, the softness of the bones, and distortion from the normal conformation. The most striking abnormality is shown in the growing region where the maladjustment presents a characteristic microscopic picture. The visible evidence of rickets is usually accompanied, and usually preceded also, by a reduction of the content of inorganic phosphorus, and frequently of calcium, in the blood serum.

As to the occurrence of rickets, it seems to be distinctly a disease of civilization, both in man and in animals. It is most prevalent where the population is most dense and where living conditions are most unfavorable, that is in cities, and among the poorer classes. So far as our information goes it is practically confined to Europe and to North America. It is absent from the oriental, tropical, and arctic countries. Savages and wild animals are free from the disease, but domesticated animals are very subject to it, though various species differ in their susceptibility. Precise evidence as to its incidence is difficult to obtain, but Schmorl[30] has stated that over 90 per cent of the children under four years of age that died in Dresden, between the years 1901 and 1906, gave evidence of rickets. In this country Hess[31]

made a report on the children in an infant asylum in New York City and noted a high incidence of this disease.

As there is a geographical distribution, there is also a seasonal incidence. Hansemann[32] noted that children dying in the fall are comparatively free of rickets while those dying in the spring usually manifest certain symptoms of it.

According to a citation by Park[33] the disease is common in pigs, lambs, kids, and puppies, but occurs less frequently in colts or calves.

For many years the cause of rickets was in dispute. It has been attributed to inheritance, to bacterial infections, to gluttony, and to disturbances in the endocrine glands. Mellanby[34] was the first to suggest that certain fats exert a protective function in bone development. He observed rachitic development in the long bones of dogs, in the epiphyses, as indicated by X-ray photographs, but when butter or cod-liver oil were included in the diet, rachitic changes were not noted. According to Mellanby, vitamin A, or some substance with similar distribution, has a distinct antirachitic effect.

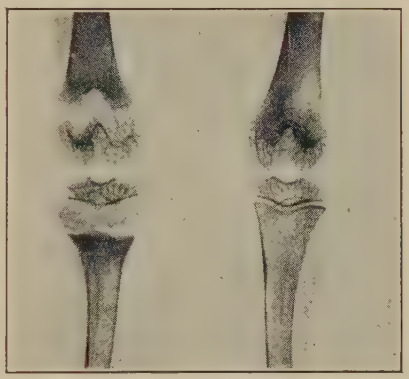


Figure 55. Cod-liver oil may prevent rickets. Note that the bones on the left are not calcified in the growing regions. After Rosenheim and Webster. By permission of the *Biochemical Journal* and the Cambridge University Press.

McCollum, Simmonds, Shipley, and Park[35] presented definite evidence that vitamin A and the antirachitic substances are distinct. The diets used were low in calcium and about the optimal in phosphorus. He noted that butter fat was of little value as a protection against rickets, but cod-liver oil was potent, even in small quantities.

Before leaving the subject we should state that the subject of

rickets is by no means closed. In the rat, for example, it seems that rickets may be prevented, if both vitamin D and ultraviolet rays are absent, by a correct ratio of mineral elements. Zucker, Johnson, and Barnett[36] have stated that by making the diet acid producing, there was protection against rickets.

II. Sunlight and Nutrition

It has been generally believed for years that sunlight has a favorable influence on the animal organism, and apparently most of our earlier ideas were advanced by clinicians. No systematic effort to study the rôle of the sun's rays, however, was made until comparatively recent times, about thirty years ago. Since then a voluminous literature has been accumulated and the subject has been studied from various viewpoints, but the mode of reaction of the living cell to light is as yet almost entirely unsolved.

In the earlier work on this topic there was much conflicting evidence, for though the rays of the sun seemed in some cases to be very favorable, there were others in which no such action was observed, and in fact darkness seemed to have no untoward results. For example, Blessing[37] made a report from observations on the *Fram* when the ship was used by Nansen on an arctic exploration. The party did not develop anemia or suffer any other bad results.

Among the earlier reports on the action of light, the one by Finsen[38] is by far the most important. In 1896 he founded a Light Institute at Copenhagen, and that organization has made notable contributions to the subject. Their chief contribution from a practical standpoint has been the successful treatment of lupus by heliotherapy.

So far as man is concerned, the visible rays of the spectrum lie between 760 and 380 $\mu\mu$, though the limits are somewhat variable. Rays of a wave length between 380 and 295 $\mu\mu$ are

absorbed by the lens, and cause fluorescence. Rays of a lower wave length are absorbed by the cornea and produce a pathological condition.

Because of the complexity of the higher animals such knowledge as we have of the action of light has been obtained chiefly by a study of single-cell organisms, and by a study of proteins. Thus it has been shown by Schanz[39] that ultra-violet rays decrease the solubility of proteins in solution. Bovie and Klein[40] exposed paramoecia to ultra-violet rays for a short period, and found that though they were not visibly affected, they were definitely sensitized to heat. If the temperature were raised to the optimum for that organism, the exposed cells were killed.

The first quantitative studies of this subject were made by Hertel.[41] He investigated the physiological action of light on single-cell organisms and showed that the lethal effect varied with the wave length of the rays. The shorter the wave length the greater its toxicity. A wave length of 232 $\mu\mu$ was distinctly toxic, while a wave length of 440 $\mu\mu$ was only slightly so.

We also know that the skin is sensitive to light, for most of us have experienced sunburn. In a practical way it has been noted that eczema and acne may be eradicated by rays of short wave length. Successful treatment of other skin affections has also been reported.

We have intimated that sunlight seems to play an important rôle in rickets, and one of the more important of the earlier reports is that of Palm,[42] who stated that rickets could be prevented or cured by sunlight. The most precise statement of our present knowledge was first given by Huldschinsky,[43] who stated that rickets can be cured by exposure to ultra-violet rays. This effect was not local, for irradiation of one portion of the body led to the deposition of calcium salts in all the bones of the body. So far as investigated, Huldschinsky's observations have been amply verified. It has been stated that X-rays have a similar action, but this has not been confirmed.

III. Prenatal Nutrition, and Condition at Birth

Thus far our attention has been directed entirely to the nutritional factors that are operative in the postnatal period. We have, tacitly at least, assumed that all the individuals were alike at birth, and that all were "normal." As a matter of fact, we are perfectly certain that individuals do differ at birth, not only in size, but also in other particulars that may have a determining influence on their postnatal history. We may therefore properly devote some attention to the nutritional factors that are operative in the antenatal stage, and consider especially the factors that influence the weight and vigor of offspring at birth. One question of both theoretical and practical interest is, what are the controllable factors that influence the well-being of young in the prenatal stage.

Are we, for example, to assume that there is a direct relation between the plane of nutrition of the mother and the weight of the young. We will first consider the case that involves merely more or less food, assuming that it is adequate in quality, but in quantity may vary from gross overfeeding to a condition of extreme underfeeding. The first possibility will receive very brief consideration, for reliable data are not at hand on this point. It is, however, the general opinion that females in excessively high condition do not produce as vigorous young as those more moderately fed. The other phase of the question, underfeeding, has received long and careful study, and the data are by no means scanty, though unfortunately they also are not concordant.

Paton[44] attempted to answer the question in an experimental way, and used guinea pigs as experimental animals. The first point to be determined was whether well-fed guinea pigs produced the same weight of young regardless of the number in the litter, and what was the proportion of the weight of young to weight of the mother.

Table II

WEIGHT OF YOUNG OF GUINEA PIGS, AS AFFECTED BY PLANE OF NUTRITION OF THE MOTHER

		Grams	*Wt. of young per gm. of mother*
	Well Fed		
I.	3 young, born June 3, weighed	210	0.35
	Mother weighed	585	
II.	2 young, born Oct. 2, weighed	200	0.40
	Mother weighed	480	
III.	3 young, born Nov. 5, weighed	225	0.37
	Mother weighed	600	
IV.	2 young, born Nov. 16, weighed	215	0.39
	Mother weighed	545	
V.	2 young, born June 4, weighed	168	0.33
	Mother weighed	505	
VI.	4 young, born Oct. 15, weighed	184	0.33
	Mother weighed	555	
VII.	3 young, born Nov. 10, weighed	221	0.30
	Mother weighed	725	
Average number of young, 2.7			0.35
	Underfed		
I.	2 young, born June 3, weighed	133	0.22
	Mother weighed	595	
II.	3 young, born Dec. 29, weighed	139	0.27
	Mother weighed	507	
III.	Young, No. not noted, born Sept. 18, weighed	120	0.25
	Mother weighed	480	
IV.	2 young, born May 1, weighed	130	0.23
	Mother weighed	639	
Average number of young, 2.5			0.248

Table II indicates clearly that the well-fed mothers produced litters of about the same weight regardless of the number in the litter. It is also evident that the underfed mothers gave birth to young that were distinctly subnormal in size.

The relation between the plane of nutrition of the dams during the gestation period, and the birth weight of the young has received considerable study at Missouri University. It is generally believed by dairymen that poorly fed cows will have

smaller calves than those that are more liberally fed. Eckles[45] divided a group of Jersey and Holstein heifers into two groups. One was fed a liberal ration from birth to first calving in order to obtain the highest possible state of nutrition. The second group was kept on a much lower plane of nutrition and at nineteen months the Holsteins in this group averaged 344 pounds lighter than those that were well fed. The lighter fed Jerseys weighed on an average 263 pounds less than those that were better fed. The calves from the lighter fed Jerseys were a little heavier than those from the better fed group. The scantily fed Holsteins produced calves which averaged two pounds lighter than those from the liberally fed group. When the comparison is made from the standpoint of weight of the young as percentage of the weight of the mother the differences are striking. For example, the calves from the light fed Jerseys had a weight of 7.4 per cent of the weight of their dams. The calves from the heavier fed Jerseys, however, had a birth weight of only 4.7 per cent of the weight of their dams. According to Eckles, breed is a much more important factor in determining birth weight than the state of nutrition of the mother during the gestation period. A somewhat similar conclusion may be reached from a study of other data reported[46] by the Missouri Agricultural Experiment Station. This group has reported the birth weight of calves produced by dams that were fed at three different nutritional levels. It is probably sufficient for our purpose to say they noted no significant differences between the calves of the high and medium plane group, either in weight or vigor. Since the number of animals in a group was small, care must be used in drawing conclusions, but it seems reasonably certain that moderate underfeeding of the mother has no adverse effect on the offspring at birth. Since the calves from severely underfed mothers were on the average below the others both in weight and vigor, it is probably a safe generalization that inferior young are more frequently produced by scantily fed mothers than by those that are adequately nourished.

This station has also accumulated considerable data (unpublished) concerning the effects of deficient nutrition of the mothers on the birth weights of pigs. Gilts of similar breeding were placed on three planes of nutrition, one well fed, one moderately underfed, and one severely underfed. It was noted that the average weight of the young from the moderately underfed sows was practically the same as that of those from the well-fed group; but the young from the severely underfed group were on the average considerably lighter than the others. It also seemed that the severe underfeeding affected chiefly the males. The males of the poorly fed group were reduced in weight about 15 per cent, while the females were reduced only about 5 per cent. As would be expected, in all groups the males were heavier than the females, and the difference was the greater, the higher the plane of nutrition.

We seldom conduct experiments that involve the health of man, and, consciously at least, never when the effects may be undesirable. During the war, however, such an experiment was conducted, more or less involuntarily, on almost a nation-wide scale in Central Europe. We are told by competent observers that the average body weight of the German population decreased markedly during the war. Underfeeding was most pronounced, of course, among the poorer classes, and so they offered exceptional opportunities for a study of the effects of severe undernutrition. A number of German physicians and physiologists have taken advantage of those opportunities, and they have published numerous accounts of their observations. In this connection we are chiefly interested in the birth weights of German children born in the latter years of the war. Much of their data was obtained from charity hospitals where presumably the more needy sought refuge, and yet, strangely enough, practically all accounts are unanimous in stating that the birth weights were not lowered by the privations undergone by the mothers. The rate of growth of these children was, of course, retarded by undernutrition following birth, but accord-

ing to these accounts, birth weights were not lowered. Up to the time of birth the hardships were all imposed on the mother, and not at all on the child. It seems to be true that severe undernutrition of the mother will reduce the size of the offspring, but only if it is extremely severe. The evidence published by Paton would seem weighty, and the data obtained at Missouri point in the same direction.

Thus far we have considered only cases where the underfeeding was quantitative, that is, the ration was adequate, but restricted in amount. We shall next pass to attempts to investigate the effects of qualitative underfeeding in which the ration was sufficient in quantity, but deficient in quality.

Observations of this type on swine have been reported by Evvard and collaborators.[47] They described an investigation in which three groups of gilts, ten in each, were fed as follows: Lot 1, corn only; Lot 2, corn and calcium chloride and calcium carbonate; and Lot 3, corn and black albumen (dried blood). In addition all animals received sodium chloride.

The observations included the weights of the total litters, the weights of the individual pigs, the number in each litter, as well as the conditions of the pigs. A summary of the weights is given in the following table.

Table III

VIGOR OF OFFSPRING

(*On basis of 100 pigs farrowed*)

Lot No.	*Very strong*	*Strong*	*Medium*	*Weak*	*Very weak*	*Dead*
1	9.52	34.92	17.46	12.71	20.63	4.76
2	23.29	24.66	24.66	2.74	8.22	16.44
3	39.19	32.43	17.57	5.41	1.35	4.05

RATION

Lot 1 . . . . . Corn
Lot 2 . . . . . Corn and $CaCl_2$
Lot 3 . . . . . Corn and "Black Albumen"

It will be noted that the average weight of the pigs from mothers receiving corn alone was lowest, that the weight of those from mothers receiving the protein supplement was highest.

The authors report that the vigor of the pigs was also markedly affected. Both calcium and protein improved the ration in this respect, though apparently the protein was most effective. It was also shown that the size of the bone (front and hind shins) was increased, though in this regard the calcium seemed most effective.

IV. Prenatal Nutrition and Postnatal Growth

It seems fairly certain then that the state of nutrition of the mother during pregnancy may have considerable effect on the weight or vigor of the newborn young. Exaggerated cases of maternal nutrition may have a decidedly adverse effect. It is, of course, obvious that apparently normal mothers not infrequently give birth to undersized and subnormal young. The question arises then, what is the relation between the condition and weight of the young at birth, to the subsequent rate of growth.

This question has been investigated by Camerer,[48] who studied the records of 138 infants, divided into three groups according to weight. The first weighed less than 2000 grams, another between 2000 and 2750 grams, and the third over 2750 grams. The weights of these were studied over a short period of time, and the percentage increment of weight was correlated with the weight at birth. He found that the percentage increment was 427 in the first group, 219 in the second, and only 195 in the third and heaviest.

It will be noted that the growth records for the infants just described represented but a few days, so the question naturally arises, What is the relation between birth weight and mature size, and also between birth weight and rate of growth? It would seem that data on this topic are not numerous, but Professor

Eckles,[15] while at the University of Missouri, made some study of the question. A number of heifers were used in a study of the normal growth rate of dairy animals. Two breeds, Jersey and Holstein, were used, and each was divided into three groups. One group was considerably below the normal birth weight, another was of average, and the third was markedly above the average birth weight. The groups, both above and below the average, were taller at two years than was the average group. There was a slight tendency, however, for the calves largest at birth to be the taller at twenty-four months.

A few cases are also presented from data available but not used in his study of normal growth. Here the tendency of those heavier at birth to be above the average in height at two years is more marked, but even in these examples the Jerseys that were underweight at birth were of average height at two years.

Table IV

RELATION OF BIRTH WEIGHT TO MATURE HEIGHT AT WITHERS

	Holstein			*Jersey*	
	Birth weight in lbs.	*Mature height at withers in cm.*		*Birth weight in lbs.*	*Mature height at withers in cm.*
Normal	89	135.8		54	125.6
Avg. of 7	69	132.6	Avg. of 6	39	124.6
Avg. of 7	88	134.2	Avg. of 8	52.9	123.8
Avg. of 5	103.8	136.8	Avg. of 5	63.2	127.1

Eckles concludes that there is little evidence of any relation between birth weight and mature size, especially in view of the large individual variations.

V. Underfeeding and Growth

Up to this point we have been chiefly concerned with what we may call qualitative factors, such as the amount and kind of protein, and of minerals; with the specific rôle of carbohydrates

and fats in the diets; and with the requirement for the unidentified nutrients, the vitamins. There is another aspect to nutrition, however, that of quantity, and for many years this phase of nutrition was the predominating one. The chief subject of nutritional investigations was the quantity of total nutrients required by the animal organism, or, perhaps more specifically, the total quantity of energy. During recent years this phase has been overshadowed by qualitative considerations, because of the newer developments in this respect. While it is necessary to recognize the unique importance of individual constituents of the diet, yet it is imperative to remember that nutrients must also be considered as a total, the entire quantity of food must at least equal a physiological minimum.

It is a general belief held by most practical live-stock producers, that superior individuals can only be obtained if they are fed liberally from birth to maturity, and that temporary retardation of growth may result in permanent stunting, at least to some degree. Obviously undernutrition may not mean the same thing in all cases; so this phase may be considered from different aspects. Thus undernutrition is affected by the age at which underfeeding occurs, by the length of the underfeeding period, and possibly by the kind of underfeeding, that is, qualitative or quantitative. Thus the supply of food may be ample, but of a kind that will not permit normal nutrition. The next point of interest then is what may be the effects of various kinds and degrees of underfeeding.

Obviously these phases must overlap somewhat, and it is impossible to study any one uncomplicated by other factors. As the first case, however, we shall consider one in which an attempt is made to inhibit all growth. We may suppose that at weaning time, or earlier if practicable, food is partially withheld from an animal so there is no further increase in weight. As will be shown later, growth does not necessarily cease when gains in weight cease. This means then that there may be an increase in the structural units proper of the body, in protein, in

mineral matter, and in water. It is equally obvious that if growth has taken place and the body weight has remained constant, there must have been a decrease in the content of body fat, and presumably of glycogen. One of the earlier attempts to maintain constant weight has been recorded by Aron.[49] He observed that puppies may be held at constant weight for several months by restricting the food supply, but ultimately the animals would die of starvation unless the food supply were increased sufficiently to permit at least some gain in weight. Stewart and Jackson made similar observations on albino rats under somewhat more severe conditions, and noted that death ultimately intervenes if the young are maintained at birth weight.

We have seen then that there is a lower limit below which the food supply cannot be reduced without disastrous consequences. We will next consider the case of an animal that receives a quantity of food sufficient to at least permit some growth throughout the experimental period, yet decidedly inadequate in amount to permit growth to proceed at the normal rate.

One of the first such studies does not answer the question entirely, as it was not continued sufficiently long to enable us to decide whether or not growth was permanently retarded. This is the work of Waters.[50] He placed fifteen yearling steers on a ration that permitted no gain in weight, and observed the resulting changes in conformation. It was noted that skeletal growth continued, the steers increased in length and height, but of course the fat reserves were depleted, and the steers became exceedingly thin.

It is then well established that even during semistarvation, true growth is by no means completely suppressed, but the chief interest is attached to the permanent consequences of underfeeding. In some respects it would be simpler to take up the more important contributions in chronological order, but for the sake of clarity it may be best to arrange them in two groups.

The first group we shall consider tends to minimize the evil consequences of undernutrition, and we shall examine these in some slight detail. The first with which we are concerned is a paper by Hatai.[51] At the age of thirty days young rats were divided into two groups, one of which received a diet limited to cornstarch and water. Obviously this was a very imperfect diet, as it must have been inadequate as a source of minerals, protein, and vitamins, and because of its unsatisfactory composition, the energy intake must inevitably have been at a minimum. The control group, of course, received a presumably complete ration. The period of inadequate feeding was three weeks, and at the end of that time the experimental animals were transferred to the complete diet. Hatai commented that the rapidity with which weight was recovered by the experimental animals was most astonishing, especially in the first three or four days. In that time they regained the weight lost during the period of starvation. Following that time gains were rapid, and apparently the period of starvation had not been followed by any permanent reduction of size.

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By way of comment we should point out that the suppression of growth did not begin until comparatively late, for a rapidly growing animal, and furthermore that the period was comparatively short. The possibility still remains that if the period had begun earlier in life, and lasted longer, the result might have been quite different.

Another contribution that should be mentioned is that of Boas,[52] on the growth of children. Experimental evidence is, of course, not available, but because of the importance of the subject his comments are included. He states that if the growth of children has been retarded by disease or other inhibiting circumstances, they will recover with extraordinary rapidity when the circumstances again become favorable. Obviously that leaves unanswered, however, the possibility that unfavorable consequences may ensue. The mature size may be reduced, the period of "youth" may be shortened, or even life itself.

We shall next consider data published by C. H. Eckles,[15] from studies made at the Missouri University. One heifer was given a liberal ration, and grew at the normal rate. Another was given a limited ration, and her growth was greatly retarded. You will note that this animal ultimately reached mature size, by lengthening the growing period. The fact seems conclusively established, that if the rate of growth is retarded, the growing period will be lengthened.

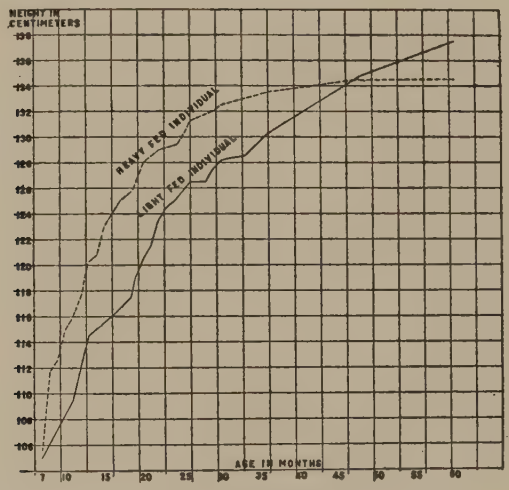

Figure 56. Compensation for slow growth by lengthening the growing period. After Eckles and Swett.

Probably the most extensive and important contributions on this topic have been made by Osborne and Mendel.[53]

Growth was inhibited, not only by quantitative underfeeding in some cases, but also in others by a ration inadequate for growth. Some contained too small a quantity of protein, some contained inadequate proteins, and others were probably deficient in vitamin B. In some of the cases they report, the period of undernutrition was both prolonged and severe, but still the experimental animals when placed on satisfactory rations finally

attained normal size and proportions. It should be noted, however, that they state that many of their attempts to induce complete recovery from retarded growth were unsuccessful. Furthermore, the stunting period was not initiated in any case until several days after weaning.

In this connection the work of Mendel and one of his pupils[54] should be mentioned. Young mice were maintained at practically constant weight for varying periods of time, and then given a generous ration. Perhaps the most striking feature of their work is the extremely rapid gain on refeeding, much more rapid than a normal animal makes at any period in its life. It would seem as if there were a tendency for the mouse underfed for twenty-seven days to grow more slowly, and perhaps it would never attain normal weight. As regards the food consumption the most striking feature is the indication that animals have some capacity of adjusting themselves to a decreased food intake. Thus as time went on the quantity of food required to maintain constant weight declined. Or if animals were held at constant weight for a time, they would again gain in weight, if the food supply were not decreased.

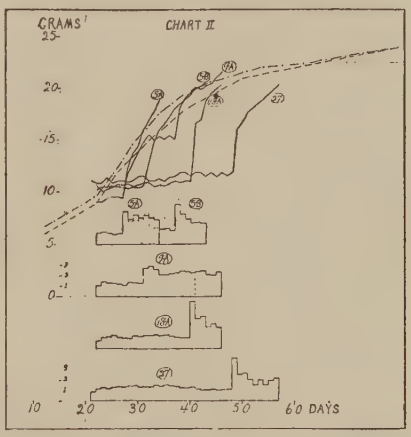

Figure 57. Retarded growth due to underfeeding may be followed by very rapid growth on refeeding. After Thompson and Mendel. By permission of the *American Journal of Physiology.*

In connection with the problem of stunting, one point is of interest. When growth is retarded, does it mean that all other phenomena, those we denote as senescence, are retarded also, or do those phenomena proceed at a normal, or only slightly retarded, rate? In other words, does retarded growth mean that

the period of youth is lengthened and that the length of the period we denote maturity is unaffected? At first thought this seems highly improbable, but some data published by Osborne and Mendel are suggestive. They state[55] that of the stock animals they observed, less than one-third lived to be two years old. Yet, of a group of stunted females they had under observation, all lived beyond that age, and all bore young at a time when they would probably have been dead of old age if they had been normally fed. It may be that the surest way of attaining long life is slowly to starve to death.

We have just discussed the data of a group of reports that would seem to minimize any untoward effects of undernutrition. In fact, Osborne and Mendel would seem to take the position that within reasonable limits the power to grow is never suppressed. One might infer from their statements that the failures to attain normal size were due to accidental causes, such as would be the more likely to attack animals in a "weakened" condition. There is, however, another group which seems distinctly to take a somewhat opposing view, that severe underfeeding in youth will be followed by unfavorable, and permanent, effects. Among the more important of these may be mentioned Aron.[49] In one experimental series he described two puppies, A and B, which were placed under observation at an age of three months. B was fed generously; A was given only a sufficient quantity to keep his weight constant. He became extremely thin, but increased in length and height until about the 200th day, when apparently no further change occurred. The author stressed the point, however, that he remained extremely active. Dog A was continued on this limited diet for about a year altogether, and at that age dogs have normally ceased growth. At that time he was measured, and his ration was gradually increased until he was given a decidedly generous ration. On the 500th day he was again measured, and the measurements were practically identical with those taken 150 days earlier, when he was in a state of emaciation. The weight at the

close of the trial was only 5440 grams, although the animal was then excessively fat. At this time the normally fed brother, Dog B, weighed 7400 grams. Aron therefore concluded that as a result of underfeeding, Dog A had lost its normal capacity to grow.

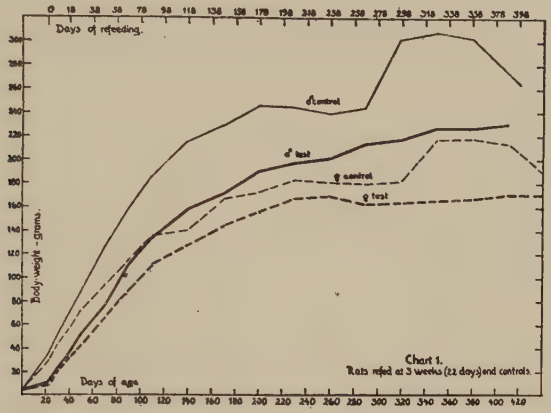

Figure 58. A short period of underfeeding, beginning at birth, may prevent the attainment of the normal adult size. Jackson and Stewart. By permission of the Wistar Institute.

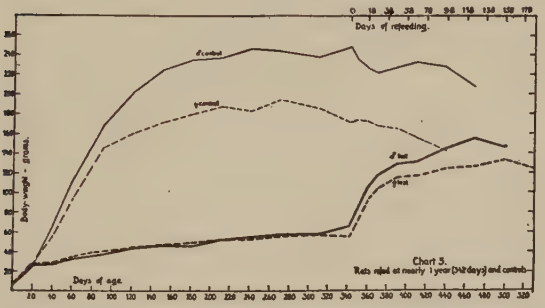

Figure 59. The underfeeding began at weaning time, and a longer period was required for the permanent suppression of growth. Jackson and Stewart. By permission of the Wistar Institute.

Jackson and Stewart are also among those who believe that early restriction of the food intake may result in permanant dwarfing.[56] They described two series of investigations carried

out on rats. In the first the underfeeding period was initiated at birth, by separating the young from the mother at various intervals. This period of underfeeding varied from three to about ten weeks. At the end of the ten-week period the underfed rats weighed about 16 grams, while the normal weight at that age is over 100 grams. Of the twenty-three rats underfed for three weeks, five equaled or exceeded their normal controls at maturity. The average, however, was distinctly lower. Of the nineteen rats underfed to about ten weeks, one female attained ultimately a weight equal to that of the controls. The others, however, were under the weights of the control animals.

The second series was placed on the deficient rations at an age of three weeks, and the period of underfeeding lasted for seventeen weeks in one group, and until the animals were nearly one year old in the other. In this latter group the average weight was about 60 grams when refeeding began. In all cases, both groups, the result was permanent dwarfing of the underfed rats. When all cases of underfeeding are considered, Jackson and Stewart estimate roughly that the dwarfing varied from about 10 per cent in the milder cases to about 35 per cent in the most severe.

It is clearly evident that the length of the underfeeding period, and the age at which underfeeding begins, are important factors in determining the extent of the injury. Aron[57] had noted that if rats were underfed from 50 to 150 days they were permanently dwarfed. Stewart[58] obtained complete recovery from underfeeding that began at three and extended to ten weeks of age. In the series of Jackson and Stewart, the effect of age is clearly demonstrated. If the underfeeding begins at birth, a period of three to ten weeks causes permanent dwarfing, but if it begins at three weeks of age a period of similar length leaves no permanent effects.

In view of the observations of Aron, of Jackson and Stewart, and of others, some earlier observations acquire added significance. Thus Dunn[59] and King[60] found that animals small at

birth are usually below the normal size at maturity. King offers the explanation, "The normal action of growth factors is inhibited from the very beginning of postnatal life by unknown constitutional causes, not by environmental conditions." It may be, however, that the small size at birth is due to interference with adequate nutrition during the prenatal state, and so is merely a case of early underfeeding. It would not be surprising if underfeeding during the fetal stage should be more injurious than during the postnatal period.

Chapter IV

Some Aspects of Form and Growth

By Clarence Martin Jackson

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SOME ASPECTS OF FORM AND GROWTH

THE changes in the form of animals during growth and development are included under the general term morphogenesis. As an introduction to the discussion of certain phases of morphogenesis in the vertebrate organism, the typical stages in human development will be reviewed briefly (Figure 60). These will serve as a basis for comparison with other animals. As in most living organisms, we begin with a single cell (A), the egg-cell or ovum. The human ovum is about one-tenth of a millimeter in diameter, or large enough to be barely visible to the naked eye. The fertilized ovum divides repeatedly to form a spherical mass of cells, the *morula* (B). (This and the next stage have not yet actually been found in man, but are inferred from their occurrence in related forms.) Fluid then accumulates within the morula, forming a somewhat distended, hollow *blastula* (C). On the upper side of the blastula, a rounded group of cells, the inner cell mass (*icm*), projects into the cavity.

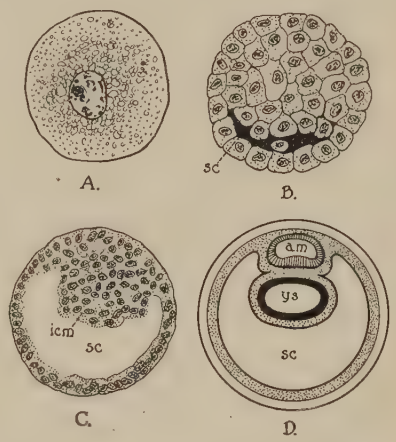

Figure 60. Early stages of morphogenesis.
A. Human ovum or egg-cell.
B. Morula with many cells, resulting from division of the ovum. A segmentation cavity (*sc*) is beginning to form.
C. The segmentation cavity (*sc*) has expanded, forming a hollow sphere (blastula), with most of the cells clumped above to form the inner cell mass (*icm*).
D. Two cavities have appeared in the inner cell mass: an upper (*am*), the amniotic cavity; and a lower (*ys*), the cavity of the yolk sac. Between these two cavities lies the embryonic disk, with the three germ layers.

Within the inner cell mass, two secondary cavities soon appear (D). The upper becomes the amniotic cavity (*am*); the lower indicates the yolk sac (*ys*). Between these two cavities

lies a flattened plate of cells, the *embryonic* disk. This disk, which represents the future body, contains three layers of cells. The upper layer, or ectoderm, will form the nervous system and the epidermis (outer skin). The lower layer, or endoderm, will form the lining of the alimentary tract. The middle layer, or mesoderm, will form the remainder of the body, including the muscles and connective tissues. The three germ layers are therefore of fundamental importance in the development of the organism.

In the next figure (61A), the membranous roof of the amniotic cavity has been removed, showing the embryonic disk viewed from above. At this stage (third week), the disk is nearly one millimeter ($\frac{1}{25}$ inch) in length, or smaller than an ordinary pinhead. A slight groove in the *primitive streak* (*ps*) is visible in the lower part of the disk. This indicates the long axis of the future body. The trunk will be formed from the region of this streak, while the upper (front) part of the disk corresponds to the future head.

Observation of subsequent stages, and especially experiments on animal embryos (to be described later), make it possible to map out on the embryonic disk what His[16] named the "organ-forming germinal areas." He worked out these areas for the chick. A similar (hypothetical) diagram which I ventured[23] to construct for the human embryo is shown in Figure 61B. This represents a somewhat later stage than 61A, since a shallow *neural groove* (*ng*) indicating the brain has now appeared in the midline of the head region.

The various regions of the body, though yet undifferentiated, are apparently already predetermined in the areas designated on the disk.* The portions near the midline belong to the back

* At first the various regions of the ovum and early embryo in general appear in many respects undetermined, and capable of developing into different structures under different conditions. The time at which the organ-forming germinal areas become fixed and predetermined varies for different organs and species. The determination is due partly to the influence of neighboring regions. For example, Spemann[46] and others find that in amphibia the formation of the neural tube

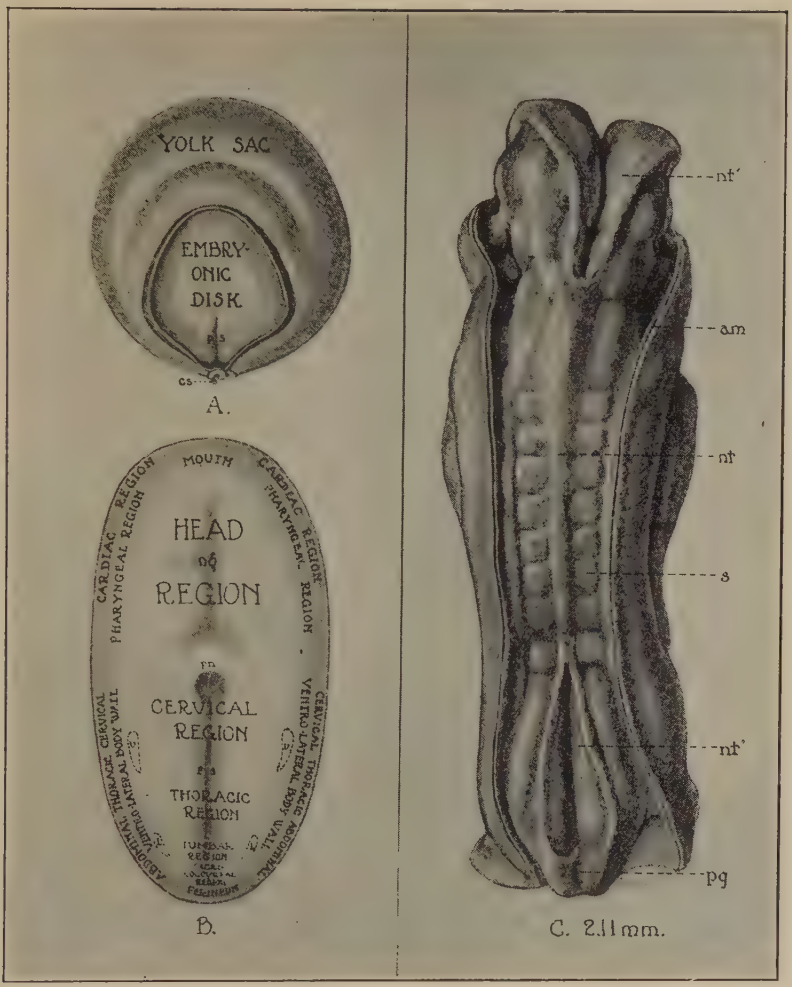

Figure 61. Early stages of the human embryo.

A. Mature ovum, after Streeter,[48] about 1 millimeter in diameter, view from above, with the amniotic roof removed to show the early embryonic disk and yolk sac. *ps,* primitive streak; *cs,* connecting stalk.

B. Diagram of the human embryonic disk at a slightly later stage, viewed from above, to show the various organ-forming germinal areas. From Jackson.[23] *ng,* neural groove; *ps,* primitive streak; *pp,* primitive pit; *pn,* primitive node; *U,* upper limb; *L,* lower limb.

C. Embryo 2.11 millimeters long, after Eternod, viewed from above, amnion removed. *am,* cut edge of amnion; *nt,* neural tube (closed); *nt', nt'',* neural tube still an open groove in brain region anteriorly and spinal cord region posteriorly; *s,* mesodermic somite, or body segment; *pg,* primitive groove (streak) and tail bud region.

or dorsal region of the body, while the outlying zone will form the future lateral and ventral body walls. The method by which the flattened embryonic disk is transformed into the body was shown by His, who was the pioneer student of developmental mechanics. Through a process of unequal growth in the different regions and constituent layers, the disk becomes gradually folded into a tube, with the upper layer of the disk forming the outer skin (epidermis), and the lower layer becoming the lining of the alimentary canal. The head and tail ends are also folded ventralward, so as to close up the ends of the tube.

I. Law of Developmental Direction

If we compare the chief regions of the body already located on the embryonic disk, it will be noted that their areas are far from proportional to the sizes of the corresponding parts which they are later to form. In the first place, the head region is relatively enormous, occupying nearly half the total area. The neck or cervical region is about half as large as the head, and the other segments of the trunk decrease progressively in size toward the tail region. In general, the embryonic head is differentiated first; and from the primitive streak region the neck, thorax, abdomen, and pelvis are budded off successively. In the second place, the area near the midline (future dorsal or back region) is relatively large; while the peripheral zone (ventrolateral body wall) is at first very small.

Growth correspondingly appears at first relatively more rapid in the dorsal head region, and less rapid in the parts located ventralward and tailward. Only gradually, through progressive changes in the relative growth rate, do the various regions of the body later attain their adult proportions. These principles may be designated as the "law of developmental direction"

from the neural groove region of the ectoderm is dependent upon the presence of the underlying ecto-mesoderm. If transplanted previous to gastrulation, the ectoderm which normally would form the neural tube may be caused to differentiate instead into other structures. Thus ectoderm may even produce somites, pronephros, or intestine, which normally come only from mesoderm or endoderm.

(Jackson[23]).* Although subject to certain exceptions and limitations, this law will be found to apply in general to the growth and development of all vertebrates.

A slightly older human embryo (Figure 61C), 2.11 mm. in length, shows the next stage, with precocious development of the central nervous system. By more rapid growth, the sides of the ectodermal neural groove enlarge as folds, which arch over and finally fuse in the midline to form the neural tube (*nt*). This tube later becomes the brain and spinal cord. The closure of the neural tube begins, not (as might be expected from the law of developmental direction) at the front end, but just behind the head, at the junction with the neck. Accordingly in the stage shown the neural groove is still open in the brain region (*nt'*), though it closes soon afterward. It still remains open also behind the neck (*nt''*), progressively closing later to form the spinal cord in the trunk region.

On each side of the neural tube in the cervical region of this embryo are also seen eight rectangular areas, the somites, or body segments (*s*). These structures in the mesoderm (middle germ layer) later form the skeleton, musculature, and other structures of the body wall. They appear first in the dorsal region, later extending around the sides into the ventral regions, with the progressive formation of the body wall. These somites are now seen in the neck, but later additional body segments will form similarly throughout the trunk region.

* As early as the fifth century B.C., the Greek anatomist, Alcmaeon,[1] noted that the head is the first part of the embryo to appear. The disproportionately large size of the embryonic head region has since been observed by many embryologists. Von Baer[8] stated that in a chick embryo of the fourth day: "An Länge betragen Kopf und Hals zusammen ungefähr so viel als der Rumpf. An Masse kommt aber der Kopf allein dem Rumpfe gleich." He later made similar observations on pig and human embryos. His[15-19] made numerous measurements establishing this principle in the chick, human, and other embryos. Jackson[20, 21] studied the question in relation to human development topography. Kingsbury[30] has recently reviewed the subject. It is of interest that cephalocaudal progression in development is characteristic, not only for vertebrates, but also for many invertebrates, especially the annelids and arthropoda.

The next figure (62) shows a lateral view of three later human embryos, all magnified to the same scale. Figure 62A represents an embryo 4.2 mm. (⅙ inch) long with the yolk sac (*ys*) and the connecting stalk (*cs*) for the attachment of the embryo. Note the relatively large head region, and the ventral curvature of the body axis. His ascribed this characteristic curvature to the resistance of the amniotic folds, which tend to prevent the direct elongation of the body; but the relative overgrowth of the neural tube and dorsal region seems to be the most important factor in producing this flexure, as was noted by Merkel.[36] The

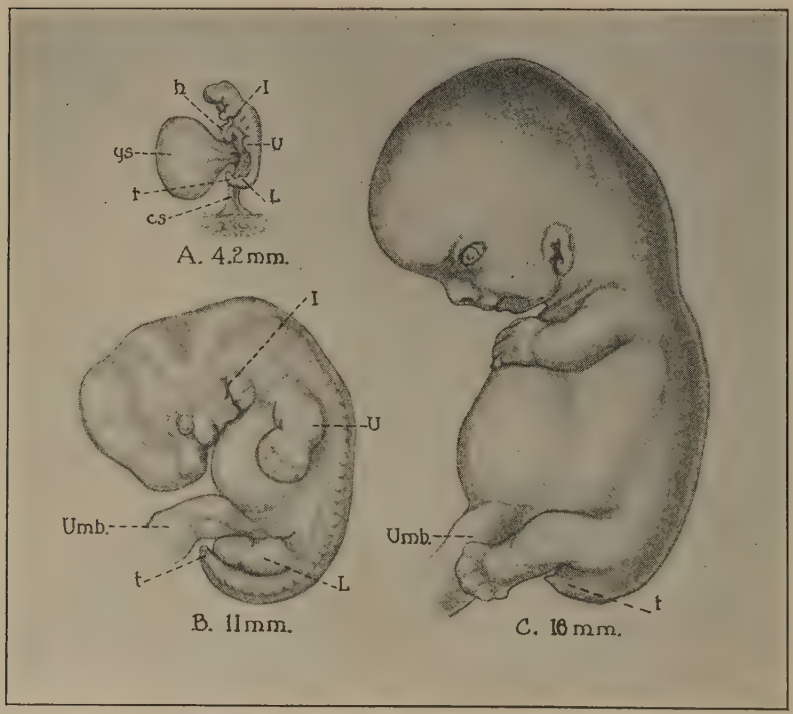

Figure 62. Later stages of the human embryo, lateral view, magnified 4 diameters. From His.[37] *I*, first branchial groove (external ear); *U*, upper limb; *L*, lower limb; *t*, tail region; *h*, heart region; *Umb*, umbilical cord.
A. Embryo 4.2 millimeters long. *ys*, yolk sac; *cs*, connecting stalk.
B. Embryo 11 millimeters long (crown-rump length).
C. Embryo 16 millimeters long (crown-rump length).

unenclosed heart (*h*) arises in the head region. It now lies just ventral to the pharynx, which is marked at this stage by three gill slits, or branchial grooves. On the lateral wall, the rudiments of the limbs (*U*, *L*) are barely visible, the upper limb appearing first.

In the next stage (62B), the embryo of 11 mm. shows a still greater body curvature, apparently caused by a continued overgrowth of the brain and spinal cord. In an embryo of this size, the volume of the brain and spinal cord is nearly three times greater than the combined volume of the organs on the opposite (ventral) side of the body axis. By the time of birth these two volumes are nearly equal; while in the adult the ventral organs are over three times larger than the brain and cord (Table 1). In addition to this body curvature, another apparent effect of the embryonic flexure in the head region, together with an expansion in the facial region, is to shove downward the heart and liver, which therefore appear to migrate along the vertebral axis from the cervical into the thoracic region. In the present stage (62B), the limbs have become larger and their chief divisions visible. Even the finger rudiments are now appearing on the platelike hand. The large eyeball and the external ear (derived from the first branchial groove, *I*) are evident, and a small but distinct tail (*t*) is visible.

An embryo 16 mm. in length is shown in Figure 62C. This approaches the end of the embryonic period, which includes the first two months of gestation. By the end of this period all of the more important organs are present, although their proportions are still far from those attained later. The head is yet comparatively large, though now decreasing in relative size. Through increased relative growth in the facial region, and in the thoracic and abdominal viscera, with a corresponding decrease in the dorsal region, the ventral flexure of the body axis is being gradually straightened out. Following the embryonic period comes the fetal period, which extends to the time of birth.

The gradual changes in the human form and proportions through the fetal and infantile stages up to the adult are shown in Figure 63. Through modifications of the growth rates in the various regions, the head and upper parts of the body become relatively smaller, while the lower parts become correspondingly larger. This process of a progressive differential growth,

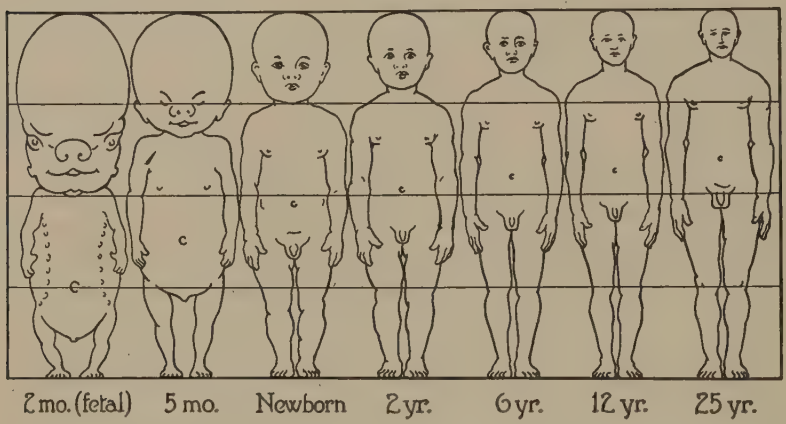

Figure 63. Changes in form and proportion of the human body during fetal and postnatal life. After Stratz.[23]

spreading wavelike from head to foot, is most strikingly shown in human development. The prolonged growth of the lower limbs is doubtless associated with the upright posture, which has been acquired by man in comparatively recent times. This posture requires a greater development of the lower extremities. But also in all other vertebrates the general law of developmental direction applies, to a variable degree, as will be shown later.

Some experiments by Peebles[40] are of importance in this connection. She opened up chick eggs and made injuries with a hot needle in various regions of the early embryonic disk (blastoderm). These injuries could be recognized when the embryo appeared in later stages of development, and thus proved what

parts of the embryo came from various regions of the disk. The results, as shown in Figure 64, confirm fully the His doctrine of organ-forming germinal areas. The horizontal line through the original center of the disk corresponds to the junction of the head and neck. The early relative growth of the head, and the

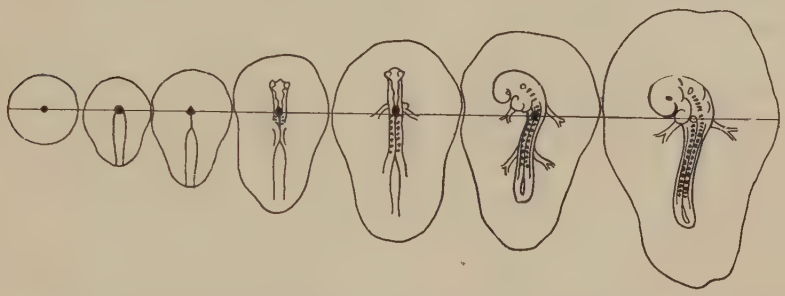

Figure 64. Location of the organ-forming germinal areas on the embryonic disk (blastoderm) of the chick, as shown by the experiments of Peebles.[40] The head region develops from the front half of the disk (upper half in the figure), and the remainder of the body from the rear (lower) half of the disk.

later gradual differentiation of the trunk (up to the third day of incubation) are also evident. Somewhat similar results were obtained by Assheton[2] and others in embryos of various species.

II. Comparative Embryonic Form

A series of embryos, representing a comparable early stage of development in the various classes of vertebrates, is shown in Figure 65. As another representative of the primates (the order to which man belongs), an embryo of a lemur (*Tarsius*) may be seen in Figure 65A. The general features resemble rather closely those of a human embryo of the same stage, the most conspicuous difference being the longer tail of the lemur embryo. Observe the same overgrowth of the head region, with progressive decrease in the size of the body as we pass tailward. The characteristic flexure of the body is also apparent.

Another mammalian embryo is that of the pig (65B), which presents the same general features as the human and lemur

embryos. Some differences already appear, however, such as a slightly larger nasal region, smaller eye and brain, larger trunk viscera and smaller limbs.

As a representative of the birds, the chick embryo (Figure 65C) likewise shows the same general form and proportions as found in early mammalian embryos. Indeed the head region, including the brain and especially the eyeball, is relatively even larger than in mammals. The enormous head is also characteristic of the reptilian embryo, as seen in the lizard (Figure 65D). This close embryonic resemblance of the birds and reptiles recalls their phylogenetic relationship, as comparatively recent descendants from a common ancestry.

Among the amphibia and fishes, the embryonic form departs more widely from the types representing the higher vertebrates. As an example of the amphibia, an embryo mud-puppy (*Necturus*) is shown in Figure 65E. Although the general features are similar to those in the preceding series, the predominance of the head region and neural tube is less marked, and the body flexure is slight. The abdominal region is swollen by the inclusion of a large mass of yolk, which is gradually consumed during later development. Similarly in the embryo of the dogfish (Figure 65F), we find the head enlargement and body flexure less conspicuous than among the higher vertebrates. There is, however, a very distinct ventral flexure in the head region.

In spite of the obvious differences in details, it is clear that these various classes of vertebrates resemble each other in their early embryonic stages more closely than later as adults. Since all the embryos in Figure 65 are drawn to approximately the same scale of magnification, it is evident that they are much alike in actual size, although the adults of the corresponding species differ greatly in this respect. From this we may conclude that in order to attain their adult size either the rate or the duration of later growth must be greater in the larger animals. To attain their adult form, it is likewise apparent that in all cases there must be a shift in the relative intensity of growth

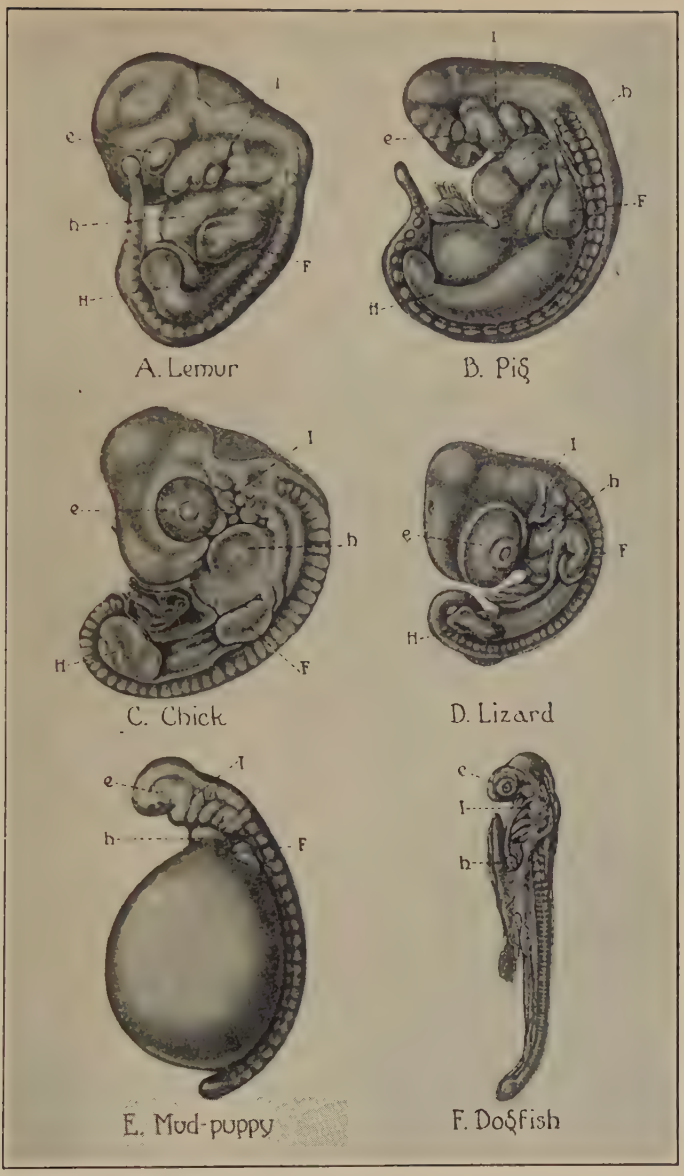

Figure 65. Corresponding early embryonic stages from a series of typical vertebrates, lateral view. Magnified about 5 diameters. *e*, eyeball; *I*, first branchial groove; *h*, heart; *F*, fore limb; *H*, hind limb. Body segments (somites) are visible throughout the trunk region.

A. Embryo of lemur (*Tarsius*), about 8 millimeters long. After Keibel-Hubrecht.

B. Pig embryo 7.5 millimeters long. After Minot.

C. Chick embryo 7.6 millimeters long. After Keibel and Abraham.

D. Embryo of lizard (*Lacertæ*) 5.9 millimeters long. After Keibel-Peter.

E. Embryo of mud-puppy (*Necturus*), about 9(?) millimeters long. After Keibel-Platt. Abdomen distended by large yolk mass.

F. Embryo of dogfish (*Acanthias*), 9 millimeters long. After Keibel-Scammon. The yolk sac has been removed.

from the head toward the tail region, in accordance with the law of developmental direction.

III. Attainment of Adult Proportions

In fishes, the observations of Hecht and others indicate that the permanent adult form and proportions are reached relatively early. For the dogfish, Hecht[13] found that in specimens 40 to 110 cm. in length the weight forms a constant fraction (.00274) of the cube of the total body length. From this he concluded that "there is a constancy of form within the species studied, which is adhered to throughout the life of the individual."

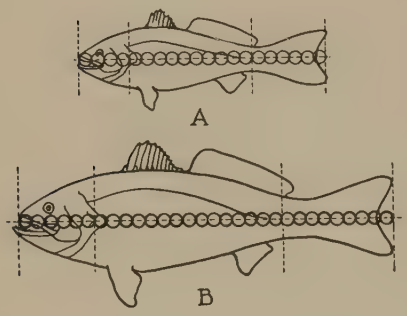

Figure 66. Showing the similarity of external form and proportions in a small fish (A) and a large fish (B). The small circles indicate a linear enlargement of one-half in the length of the body and parts of the larger fish. After Hecht.[14]

Later, Hecht[14] investigated a series of eleven species (seven families) of bony fishes at different sizes. He found here likewise that, for the sizes observed, there are in each species definite and constant ratios between total body length and the lengths of the head, trunk ("body"), and tail, as well as the width and depth of the body. As shown in Figure 66, this means that a small fish (A) has the same body form as a large fish (B), all parts in the latter being enlarged proportionately. The data for one species (*Anchovia*) are shown in graphic form in Figure 67. The "curves" for the various dimensions are all of the straight-line type, according to the formula

$$y = cx$$

where y is the linear dimension of any part, x the corresponding total body length, and c a constant fraction for the given part.

Hecht recognized that this rule does not apply to the viscera, whose varying growth rates in the dogfish had been shown by Kellicott.[29] Kearney's[27] data also show that the constant relation between body length and body weight does not hold for dogfish less than 30 cm. long, which would probably correspond to a year of age (Kellicott). Hecht furthermore noted that the early attainment of a constant external form occurs only in vertebrates with indeterminate growth, *i.e.*, with no fixed limit of adult size (as is said to occur in fishes and amphibia); "whereas in animals having determinate growth, the external form changes continually during the period of growth, and as soon as the form becomes constant, growth ceases." He also concluded that this early constancy of form in the fishes is an adaptation to aquatic life.

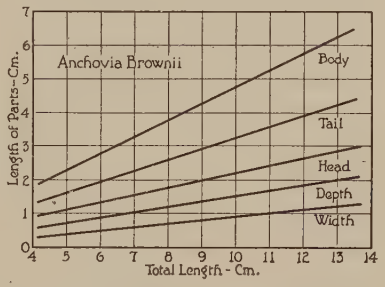

Figure 67. Graph showing the relations between total length and various linear dimensions in the fish, *Anchovia brownii*. The individual measurements, grouped closely along the straight lines, according to the formula: y (length of part) $= c$ (constant fraction) times x (total body length). After Hecht.[14]

Apparently but few measurements have been made showing changes in the external form of amphibia. Donaldson and Schoemaker[11] observed that in frogs from one year of age to adult the leg-bone lengths bear a nearly constant ratio to the body length. This would imply constancy of form at least in this one feature.

We may compare the growth in external dimensions of the fish with the growth found by Calkins and Scammon[6] in the human fetus (Figure 68). They constructed graphs to show the relations of total body length to about 70 linear dimensions of the fetal body. Nearly all these present a straight-line relationship, as shown by four typical cases in Figure 68. The 70 measurements may be grouped into three general classes. The first group includes the thoracic dimensions (exemplified by chest

depth in Figure 68), according to the general formula: $y = cx$. This signifies a relationship like that previously shown for the fish. The thoracic dimensions accordingly remain in constant proportion to body length, during the fetal period. The second group includes head and neck dimensions (exemplified by head length in Figure 68), according to the general formula: $y = cx + b$. In this case, although each dimension is increasing in proportion to the body length during the fetal period, the positive b indicates a relatively larger size during the preceding embryonic period. The third group includes in general the pelvis and extremities (exemplified by pelvic width and foot length in Figure 68), according to the general formula: $y = cx - b$. In this case, although the dimensions are increasing in proportion to the body length during the fetal period, the negative b indicates a relatively smaller size during the preceding period.

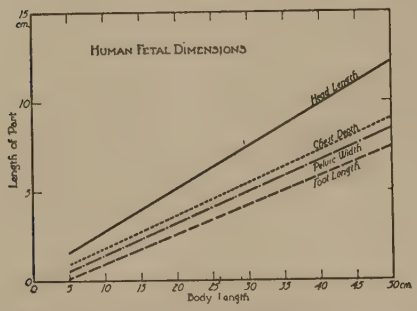

Figure 68. Graph showing typical external dimensions during the human fetal growth period. Data from Calkins and Scammon.[6]

On first thought it might seem that, since all external dimensions are increasing uniformly in relation to body length, the body form should remain constant during the fetal period. This applies only to the thorax, however. On account of their relatively greater initial size, the head and neck dimensions are becoming relatively smaller; while the reverse is true for the pelvis and extremities.

The changes in proportional growth in various parts of the body axis are also clearly evident in Figure 69, showing the percentage length of various regions in the human vertebral column at different stages of development. The thoracic region remains fairly constant at slightly less than 40 per cent of the column from the early embryonic to the adult stage. The cervi-

cal region decreases nearly half in relative length during the same period. This is counterbalanced by a relative increase in the lumbar and sacral regions. The coccygeal (caudal) region is variable, but in general decreases in relative size, in accordance with the rudimentary development of the tail in man. Calkins[5] found that the characteristic regional differences in growth of the vertebral column apply likewise to the growth of individual vertebrae within each region.

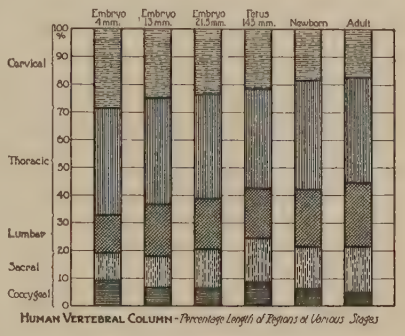

Figure 69. Histogram illustrating the changes in the relative length of the various regions of the human spinal cord at different stages—embryonic, fetal, newborn, and adult. Data from His[17] and Jackson.[21]

Scammon[6] has demonstrated similar progressive changes in the weights of the head, trunk, and extremities, thus confirming the law of developmental direction for growth of these parts during the human fetal period.

IV. Relative Growth of Systems and Organs

Having noted the relative growth rates for the chief divisions of the body, we may next observe the growth of the principal constituent organ systems. Some data on the relative weight of the chief systems in the newborn and adult stages of a few typical vertebrates are given in Table I. The skin of the dogfish decreases from about 11 per cent of the body weight at birth to 7 per cent in the adult. In the chick, guinea pig, rat, and man the relative weight of the skin in the newborn appears nearly the same as in the adult (including the subcutaneous tissue in man). However, this does not necessarily mean that the skin remains in constant proportion to the whole body throughout the entire postnatal period. In the rat, for example, although not shown in the table, the skin grows rapidly in the first week after birth, reaching a temporary maximum of nearly

Table I

PERCENTAGES OF TOTAL BODY WEIGHT FORMED BY VARIOUS PARTS IN NEWBORN AND ADULT STAGES OF DIFFERENT SPECIES

Based on data from Bessesen and Carlson, Jackson,[20, 22] Jackson and Lowrey,[26] Kearney,[27] and Latimer.[31]

	NEWBORN					*ADULT*				
Part	*Dogfish*	*Chick*	*Guinea pig*	*Rat*	*Human*	*Dogfish*	*Chick*	*Guinea pig*	*Rat*	*Human*
Skin	11.3	10.9*	18.0	19.8	19.7†	7.0	10.9*	17.0	18.0	17.8†
Ligamentous skeleton	8.6	15.7	10.0	17.3	17.0	9.2	11.0‡	7.0	10.9	17.0
Musculature	45.0	22.0	32.0	24.4	25.0	63.0	47.0	33.0	45.4	43.4
Brain, cord, and eyeballs	3.6	5.6	3.6	6.0	13.4	0.9	0.5	0.7	0.9	2.3
Viscera	7.4	21.4	15.3	12.1	11.1	8.4	8.3	10.0	12.4	7.7
Remainder	24.1	24.4	21.1	20.4	13.8	11.5	22.3	32.3	12.4	11.8
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

* With feathers. Weight without feathers remains nearly constant at 8.9 per cent throughout the postnatal period.

† Data from Vierordt. Includes subcutaneous tissue.

‡ Relative weight for male; 8.0 per cent in female.

26 per cent of the body weight. There is a similar postnatal increase in the chick, although the relative weight of the skin without the feathers remains nearly constant.

The difference between the sum of the relative (percentage) weights of all the organs weighed and the total body weight (100 per cent) is indicated in the table by the last item, "Remainder." This item includes various smaller unweighed structures, intestinal contents, fat and connective tissues, loss of fluids, etc. This factor in the newborn appears fairly uniform in all except the human. In the adults, however, it varies from 11.5 per cent in the dogfish to 32.3 per cent in the guinea pig. It must be kept in mind that variations in this amount will necessarily affect the relative weight of all other parts. This, for example, will account for some peculiarities in the relative size of organs in the guinea pig, as compared with the other species. These differences are perhaps more clearly apparent in the graphs for the various systems.

Some graphs will now be presented to illustrate the changes in the relative size or weight of various parts in typical vertebrates during prenatal and postnatal life. In these graphs, the time element is disregarded, and the purpose is merely to show the variation for different species at certain stages: in early embryonic life, at the time in the prenatal period when the parts reach their maximum relative size, at birth, at the period of postnatal maximum relative size, and in the adult stage. The data in many cases are not strictly comparable, and are only approximate; but they will serve to indicate roughly similarities and differences in the relative growth of various parts of the body.

The relative weight (or volume) of the head is shown in Figure 70. The human head increases from about 35 per cent of the body in the earliest embryo measured to a maximum of 45 per cent somewhat later. Thereafter it grows more slowly than the body as a whole, and decreases in relative size, forming about 25 per cent at birth and only 7 or 8 per cent in the adult.

The head of the pig shows a smaller prenatal increase, and remains relatively smaller than the human head at all stages of the life cycle. The dogfish head is relatively slightly smaller than the pig's head in the early embryo, but increases to a much larger maximum relative size soon afterward. The dogfish head likewise remains relatively smaller than the human head throughout the prenatal period. (This dogfish, *Mustelus canis*, is a viviparous form.) The head of this fish reaches its adult proportion, about 12 per cent of the body weight, at a comparatively early postnatal stage, however. This is relatively larger than the adult human head. Quantitative data for the guinea pig, chick, and rat are available for the postnatal period only. The relative size of the head in the guinea pig appears closely parallel with that in the dogfish. In reality it does not reach the minimum until adult size in the guinea pig, while the adult proportion is reached much earlier in the dogfish, as before mentioned. The head in the postnatal chick is relatively much smaller than in the other species. It is also characterized in the adult by a distinct sex difference. The head is relatively larger in the cockerel, due chiefly to the comb and wattles. The rat shows a marked peculiarity which has not been noted in the other species. The maximum postnatal relative size of the head occurs, not at birth, but at a slightly later period, after which it decreases gradually to the typical adult relation.

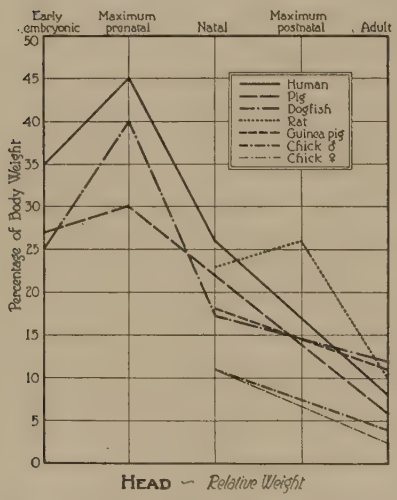

Figure 70. Graph showing changes in the relative weight of the head in different species at various stages, prenatal and postnatal. Data from Bessesen and Carlson, Kearney,[27] Jackson,[20, 22] Jackson and Lowrey,[26] Lowrey,[35] and Latimer.[31]

Some data for the relative weight of the moist ligamentous

skeleton are shown in Figure 71. Weights for the prenatal period are available only for the dogfish. In this case, there appears to be a slight increase in the relative weight of the skeleton, reaching a maximum of 10 per cent shortly after birth, and decreasing slightly in the adult. The guinea pig presents a somewhat greater relative decrease in skeletal weight between birth and adult stage. In the other species, the skeleton at birth appears relatively much heavier. In both rat and chick, there is a slight relative increase after birth, with a marked decline in the adult. The chick shows also a distinct sex difference, the skeleton being relatively heavier in the adult male. The human skeleton apparently remains nearly constant in relative weight during the postnatal period, although but few observations are available.

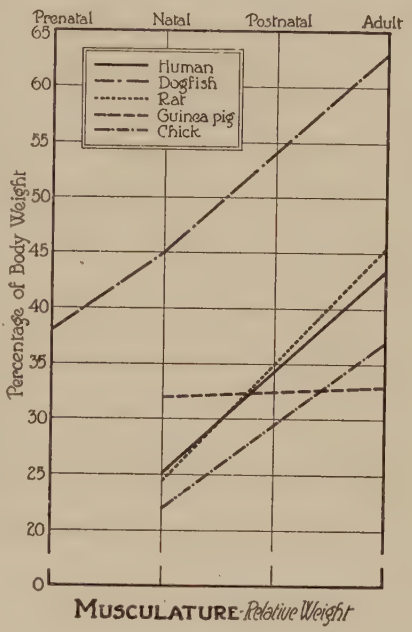

Figure 71. Graph showing changes in the relative weight of the musculature in different species at various stages, prenatal and postnatal. Data from Bessesen and Carlson, Jackson,[20, 22] Jackson and Lowrey,[26] Kearney,[27] and Latimer.[31]

Strikingly different relations appear in the musculature (Figure 72). One might have expected a closer correlation with the skeleton, on account of their functional relationship. The guinea pig appears exceptional, with but slight change in the percentage weight of the musculature during the postnatal period. The others present a very striking increase. The musculature appears relatively most poorly developed in the chick, intermediate in rat and man (which have nearly the same percentage of muscle), and relatively much greater in the dogfish. During the prenatal

period, the relative weight of the musculature in the dogfish is less than at birth. This is apparently true also for the other forms, although quantitative data are scarce.

The progressive increase in the relative size of the musculature, together with its large bulk, accounts in part for the tendency to decrease in the relative size of other structures, such as the nervous system and the viscera. The marked decrease in the relative size of the brain (which parallels that of the head) is shown in Figure 73. At the beginning, the chick brain seems to be relatively the largest of all, though exact data for the earlier embryos are lacking. At the ninth day of incubation the brain of the chick forms about 28 per cent of the body (Welcker and Brandt), decreasing to less than 3 per cent at hatching, and to one-sixth of 1 per cent in the adult. Aside from the early chick, the human brain appears relatively largest at all stages, decreasing from about 22 per cent in the embryo to 12 per cent at birth and 2.2 per cent in the adult. The brain of the dogfish is in the embryo relatively larger than that of the pig; at birth the pig brain is relatively larger, but in the adult they are nearly equal (less than 0.1 per cent). The rat shows a temporary postnatal increase in the relative size of the brain similar to that for the head and skeleton. The guinea-pig brain (not shown in the figure) decreases steadily from 2.6 per cent of the body at birth to 0.044 per cent in the adult.

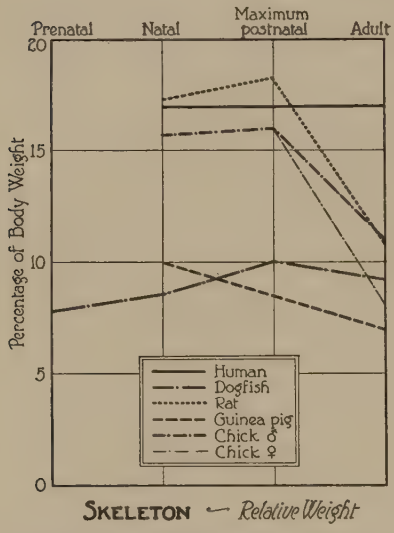

Figure 72. Graph showing changes in the relative weight of the skeleton in different species at various stages, prenatal and postnatal. Data from Bessesen and Carlson, Jackson,[20, 22] Jackson and Lowrey,[26] Kearney,[27] and Latimer.[31]

The thoracic and abdominal viscera as a group (Figure 74) appear more irregular in relative size. Of the three species for which prenatal data are available, the viscera of the pig are relatively much larger than those of man and dogfish. In all three the viscera at first increase in relative size, then decrease to birth. From birth to adult, the viscera in man and pig decrease, remaining closely parallel with each other. In the chick, the viscera are in the early postnatal period relatively much larger than in the other animals. In the chick, rat, and dogfish, there is also a postnatal increase to a temporary maximum in relative visceral size (weight), and in the last two the adult thoracic-abdominal viscera appear relatively slightly greater than at birth.

The weight curves for the whole visceral group are of course dominated by the larger organs, especially the alimentary tract, heart, lungs, and kidneys. This obscures the fact that there are very marked differences in growth among the individual organs in all

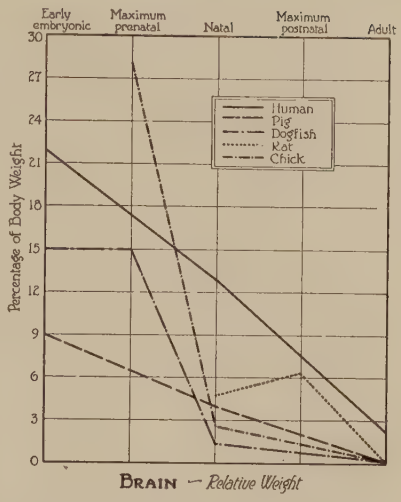

Figure 73. Graph showing changes in the relative weight of the brain in different species at various stages, prenatal and postnatal. Data from Bessesen and Carlson, Jackson,[20, 22] Kearney,[27] and Latimer.[31]

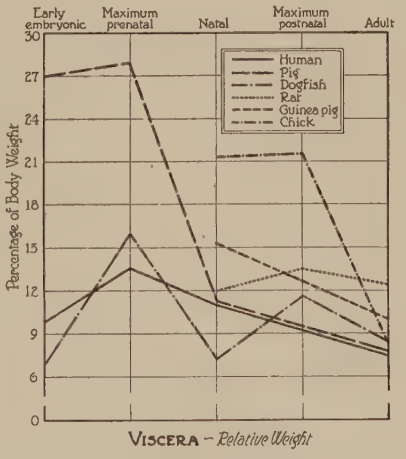

Figure 74. Graph showing changes in the relative weight of the viscera (thoracic and abdominal group) in different species at various stages, prenatal and postnatal. Data from Bessesen and Carlson, Jackson,[20, 22] Jackson and Lowrey,[20] Kearney,[27] Latimer,[31] and Lowrey.[35]

species. As an example, some observations by Scammon on human growth will be cited. In the next chart (Figure 75) curves are drawn to represent the percentage growth of the human body and viscera during the prenatal and postnatal periods. The horizontal base line (abscissa) indicates the age, and the verti-

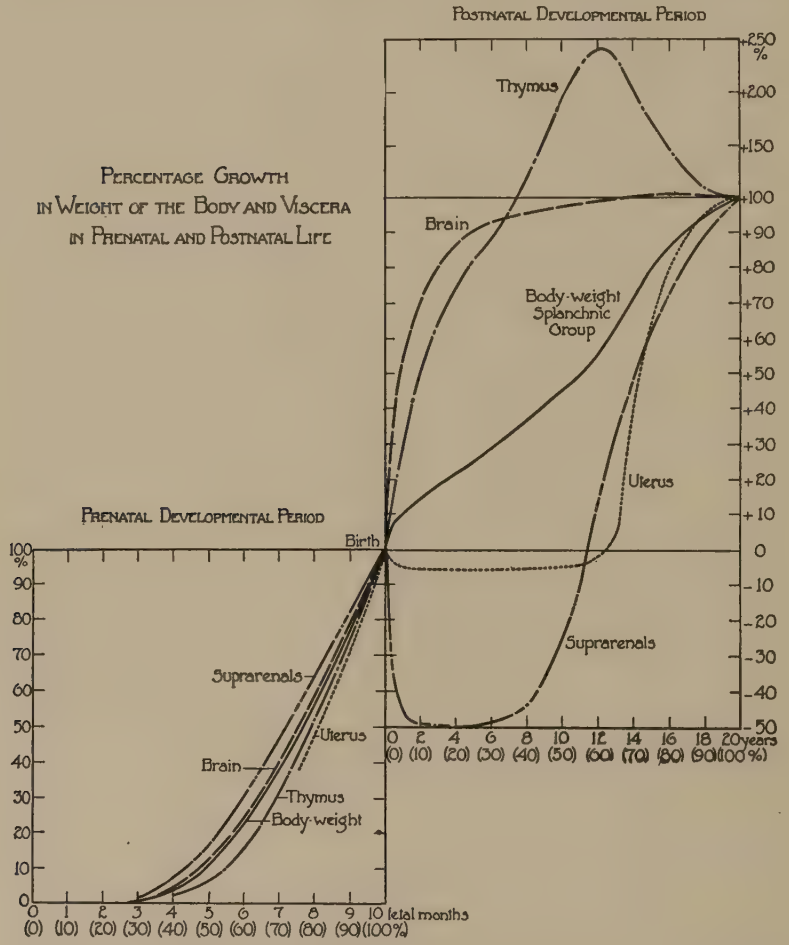

Figure 75. Graph showing relative (percentage) growth in weight of the human body and viscera during fetal and postnatal life. The horizontal base line (abscissa) indicates age; vertical distance (ordinate) indicates the percentage of the weight at the end of the period, prenatal or postnatal, which has been reached at the corresponding age. Unpublished graph by R. E. Scammon.

cal distance (ordinate) the percentage of the final weight (prenatal or postnatal) reached at the corresponding age. Thus in prenatal growth the suprarenal glands and brain appear somewhat precocious; while the uterus and thymus lag below the body weight curve, rising by more rapid growth in the latter part of the prenatal period. In general, however, the relative growth of the various organs appears more uniform in the prenatal (fetal) period than later.

In the postnatal period, we may note first the curve for the body weight and splanchnic group (most of the viscera). This curve shows in general an initial steep ascent, corresponding to the rapid growth in infancy. This is followed by a long phase of steady but slower increase during childhood. At the age of puberty, there is a second increase, tapering off more slowly to nearly adult size at twenty years of age.

Several organs and systems, however, depart more or less widely from this prevailing type of growth, and four extreme cases are represented on the chart. Two of these organs, the brain and the thymus, are precocious in their growth, increasing more rapidly in the earlier part of the postnatal period, and slowing up later. The brain has nearly reached its adult size at six years, and is full-grown at fifteen. The thymus continues to increase steadily until the age of puberty. After this it decreases, not only relatively but absolutely, so that its adult weight is less than half the maximum at puberty.

On the other hand, the suprarenal glands undergo after birth an involution with actual loss of half their absolute birth weight. This loss is made good by more rapid growth in late childhood and adolescence. There is also a slighter postnatal loss in weight of the uterus, which remains relatively small during childhood, but grows with extreme rapidity at the age of puberty.

While there are many variations in the character of postnatal growth among the individual organs, Scammon[43] has grouped them (with a few exceptions) under four types, as shown in

Figure 76. First we have the *general type*, which includes the skeleton, musculature, and many of the thoracic and abdominal viscera. Since these structures constitute the chief bulk of the body, their combined growth curve necessarily conforms closely to that of the body as a whole. The reproductive organs follow the *genital type*, with slow growth during childhood and rapid acceleration at puberty. The opposite tendency is seen in the *neural type*, which includes the brain, spinal cord, eyes, and many other head structures. Here we have more rapid growth during infancy and childhood, so that the adult size is reached early, and growth practically ceases before the age of puberty. Finally the *lymphoid type*, including the lymph glands, thymus, etc., through early rapid growth reaches a maximum size about the age of puberty, with a marked decrease later in both relative and absolute weight.

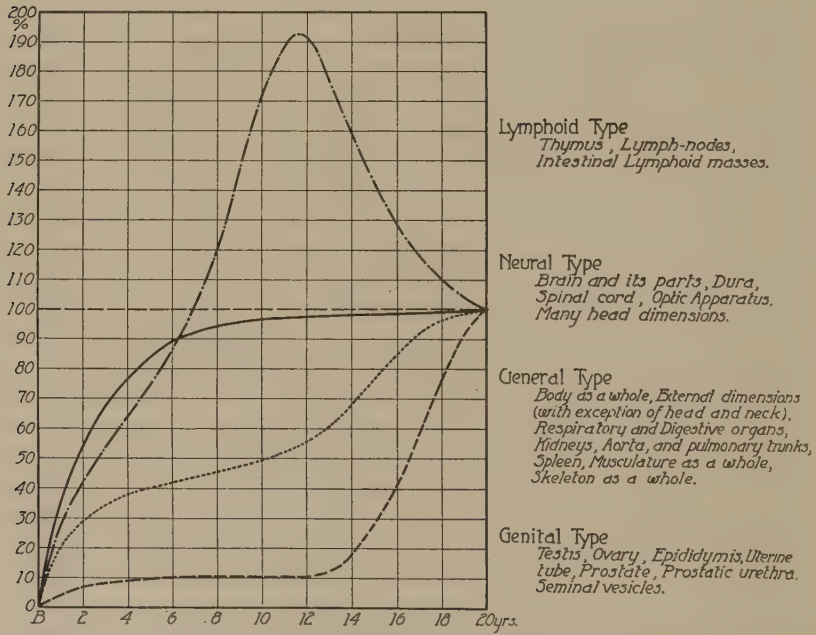

Figure 76. Graph showing types of human postnatal growth. The horizontal base line (abscissa) indicates the age; the vertical distance (ordinate) indicates the percentage of the final weight which is reached by each type at the corresponding age. Scammon.[43]

V. Relative Growth of Organ Parts and Tissues

It is evident from the foregoing data that the growth of the body as a whole is the resultant of quite variable simultaneous growth rates in various parts, systems, and organs. The law of developmental direction evidently does not apply equally to all the structures in a given region. A further analysis of the growth process reveals a similar lack of uniformity even within the individual organs. A few examples will be cited. In the human brain, it has been shown by Dunn[12] and Scammon[45] that the fetal brain stem is relatively precocious in growth; while the cerebellum at first lags behind, increasing in relative size through late fetal and postnatal periods. Stewart[47] found a similar relation in the postnatal growth of the brain in the rat. Miller[38] observed marked differences in growth of the gray and the white matter of the human spinal cord; and Scammon and Armstrong[44] similarly noted varying growth rates for the constituent parts of the eyeball.

In the hypophysis (pituitary gland) of the rat, Jackson[24] found that during postnatal growth the pars anterior becomes relatively larger, the pars posterior smaller, while the pars intermedia remains unchanged in relative size. (Rasmussen[41, 42] and Covell[9] found somewhat different relations in the human hypophysis.) Similarly in the suprarenal gland, the cortex becomes relatively much larger, the medulla correspondingly smaller (Jackson[25]). In the case of these two organs, the analysis was carried still farther, showing different growth rates in the constituent tissues and cells (Table II). In some regions there is an increase in the relative amount of epithelial parenchyma, in others a decrease, in comparison with the supporting tissue (connective tissue stroma) and blood vessels. Finally the same table includes some volumetric data on the corresponding cells, showing changes in relative proportions of the cell nucleus and cell body (cytoplasm). There is in all cases a marked reduction in the nucleus-plasma ratio between newborn and adult stages. Similarly variations in tissue and cell growth probably occur to

a variable degree in all organs. Especially the relative amount of stroma varies according to age.

Table II

VOLUMETRIC CHANGES IN THE CONSTITUENT TISSUES AND CELLS OF THE HYPOPHYSIS AND SUPRARENAL GLANDS IN THE ALBINO RAT, NEWBORN AND ADULT

Jackson[24, 25]

Hypophysis (pars anterior)	*Newborn* Per cent	*Adult* Per cent
Parenchyma	93.3	89.4
Stroma and blood vessels	6.7	10.6
Cytoplasm of parenchyma cells	66.0	80.0
Nuclei of parenchyma cells	34.0	20.0
Suprarenal Cortex (average)		
Parenchyma	87.7	86.6
Stroma and blood vessels	12.3	13.4
Cytoplasm of parenchyma cells	66.6	82.4
Nuclei of parenchyma cells	33.4	17.6
Suprarenal Medulla		
Parenchyma	67.2	72.3
Stroma and blood vessels	32.8	27.7
Cytoplasm of parenchyma cells	54.0	90.4
Nuclei of parenchyma cells	46.0	9.6

VI. Cell Changes in Development

The analysis of the growth process thus leads us back to our starting point, the cell. Morphogenesis, like other vital phenomena, becomes ultimately a cell problem. While time permits only a brief consideration of the cell changes during development, a few of the more important aspects may be mentioned. These include the related cell changes in (1) number, (2) form, (3) position, (4) size, and (5) structure.

1. *Cell number.* With reference to cell division, Bizzozero[4] classified the cells of the body under three types—permanent,

stable, and labile. In the *permanent* cells, of which nerve cells and striated muscle are examples, cell division (mitosis) usually ceases rather early in prenatal life, and the number of these cells then becomes fixed and constant. In the *stable* cells, which include those of most organs, division continues for a longer period, sometimes (to a slight extent) even up to the adult stage. The *labile* cells continue division throughout life, replacing losses in those tissues which are constantly worn off or used up, such as the surface epithelia and the blood cells. In these cells, growth is chiefly by division or hyperplasia, but the total number of cells becomes fairly constant as soon as there is an equilibrium between cell production and cell destruction.

Many observers have noted that cell division (mitosis) is very active in the most rapidly growing embryonic regions. This indicates in these regions a greater cell activity and cell metabolism, which has been demonstrated by Child[7, 8] and his coworkers by means of various physiological tests. Minot[39] used the term "mitotic index" (number of mitoses per thousand cells) as a measure of the intensity of growth in various parts of the embryo at different stages. Milone[37] has recently applied this method in an interesting study of the growth of the spinal cord in bird embryos of different species. Levi[34] and others have noted the curious fact that mitosis in embryonic tissues is not uniform in rate, even in the most actively dividing cells. There seems to be a tendency to rhythm in the process, with alternate periods of relative rest and activity.

2. *Cell form.* In some cases, especially in the earlier stages of development, cells may change their form without change in number or size. They may flatten, elongate, or otherwise change in shape. This may result in a regional change in form without increase in total mass, which corresponds to the plastic type of growth (Pfeffer).

3. *Cell position.* Cells may also change their position by individual migration. This occurs, for example, in the embryonic development of the sympathetic nervous system, and is con-

tinued throughout life by the wandering cells of the blood. This process is distinct from that in which whole organs are mechanically displaced, due to unequal growth in neighboring regions, as before mentioned for the heart and liver.

4. *Cell size.* In general, the cells remain relatively small so long as cell division continues. After cells have ceased to divide, they usually undergo more or less enlargement or hypertrophy during the growth period. Levi and others, however, have noted that large animals differ in size from small animals chiefly in the total number of cells in the body rather than in size of cells. Aside from cells of the permanent type (especially nerve and muscle cells), there is relatively little difference in the size of individual cells between the mouse and the elephant.

5. *Cell differentiation.* While the embryonic cells continue dividing, they remain in general not only small but also relatively poor in cytoplasm and simple in structure. The succeeding period of cell enlargement is also accompanied by a specialization in structure and function, with a loss of capacity for cell division. This rule holds in general throughout the body, although the time and manner of the cell specialization vary greatly among the constituent parts, organs, tissues, and cells. Minot described the life history or cytomorphosis of every cell as a cycle with various stages. Each cell passes through an early undifferentiated stage, followed by a stage of differentiation and final stages of death and removal. But differentiation begins much earlier in some cells than in others, and the length of the life cycle also varies from a few days in some cells to many years in others. Cells in all stages of cytomorphosis can therefore be found in the body at all ages, although the proportion of undifferentiated cells decreases progressively during development. In the adult organism, relatively few undifferentiated cells remain, forming the labile type before mentioned.

We may therefore distinguish, for the body in general as well as in the individual organs, three periods of growth. First comes the embryonic period of growth by numerical increase

(hyperplasia) of cells. This is followed by a second stage in which some cells continue division, while others cease dividing and enter on the period of differentiation and enlargement (hypertrophy). In the final period growth is almost entirely by hypertrophy alone.

VII. Underlying Factors of Morphogenesis

Finally comes the question as to the underlying factors of morphogenesis. What causes the developmental cell changes associated with growth and differentiation? This problem is too complex and difficult for brief consideration. It may be noted, however, that both intrinsic (hereditary) and extrinsic (environmental) factors are involved. The intrinsic or hereditary factors are expressed chiefly through the nuclear organization (chromosomes) of the fertilized ovum, but to some extent also in the cell body or cytoplasm. The extrinsic or environmental factors include the essential nutriment, oxygen, heat, light, and other external conditions necessary to development.

As soon as cell division begins, *i.e.*, in the morula stage, the mutual influence of the individual cells introduces a new and important set of forces, which may be termed the correlative factors in development. Each cell henceforth is influenced by its neighbors in various ways. There are *physical* effects, through spatial relations, contact, pressure and tension, and similar factors. These have been admirably reviewed by D. W. Thompson.[49] Then there are *chemical* effects, doubtless present from the beginning through the products of cell metabolism, such as the "trephones" of Carrel or the autocatalytic agents of Robertson. Later specific hormones are produced, especially in the well-known system of endocrine organs or ductless glands. Finally the developmental process is influenced by *neural* effects. Stimuli transmitted by the nervous system affect metabolism and morphogenesis chiefly through functional hypertrophy and differentiation of the cells involved.

There has been much discussion and controversy over the

essential nature of the mechanism controlling the developmental process. Is morphogenesis primarily the result of *structure* or of *function?* Arguments of varying plausibility have been offered on both sides of the question. Roux held that the functional factor is important only in the later phases of morphogenesis. It seems to be largely a question of definition of the terms structure and function. My own view is in agreement with those who hold that in a broad sense the two are inseparable and indispensable. As expressed by Wallis,[50] "Function is only structure in action, but the structure which is not in action is about as futile as the function which has no substratum."

Both physics and chemistry are now interpreting material phenomena in terms of structure,—molecular, atomic, and electronic; but with this structure there are always associated energy and movement, which correspond to function. Similarly in the living organism we have to deal ultimately with the arrangement and the movements of material particles, *i.e.*, with structure and function reduced to their lowest terms. And therefore, as it seems to me, in solving the problems of morphogenesis we have both need and ample room for coöperation among biologists and others interested in all of the various aspects of the question. It is a problem primarily for the morphologists and the physiologists; but they need also the help of mathematics, physics, and chemistry. It is a fascinating field of great importance in which we may all join hands as "companions in zealous research."

Chapter V

Physiological Factors Regulating Normal and Pathological Growth

By Charles Wilson Greene

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PHYSIOLOGICAL FACTORS REGULATING NORMAL AND PATHOLOGICAL GROWTH

AN analysis of growth from the causal standpoint is exceptionally difficult and in many respects impossible. Living protoplasm of both plants and animals possesses the power to add to its mass more living substance similar in kind. The scientific attitude was expressed by Dr. Mendel speaking from this platform when he described certain inherent properties of living substance as "the growth impulse." This phrase is a recognition of the ancestral origin of the chemical or physico-chemical properties of living protoplasm.

"The growth impulse" in an embryo plant or animal adequately supplied with foods and food vitamins is manifested by an orderly but infinitely complicated series of changes in which there is a fairly definite and average cycle of increase in mass, an unfolding of characteristic form, and an intricate differentiation of parts all according to laws that have been presented in preceding lectures before this audience. The nature of these changes, the time of the growth cycle, the relations of environment and of foods, and the story of the embryological and tissue components—all have been presented. What remains to be discussed is the coincident functional or physiological factors influencing growth.

We recognize that during the growth in size, and occurring hand in hand with differentiation in structure, there is an orderly unfolding of function, a differentiation of physiological labor, so to speak. Capacity to function in different ways and to different degrees appears in orderly sequence, and the functional acts and processes at once become a part of the environment which henceforth conditions the further development of the individual, both morphologically and physiologically.

It is not altogether easy to express, or in fact to determine, these functional factors. The example of developing muscle may help to explain. When a muscle is stimulated to contract, it liberates energy in the form of electricity, heat, and mechanical work. In the physiological act of contraction complex chemical reactions occur with greater intensity than in the normal resting muscle, and chemical by-products are formed in augmented amounts. These steps change the physical constants of the muscle protoplasm involved. There is an after-readjustment of the water content of the muscle, of the percentage relations of the nutritional elements in its environment, of the hydrogen and other ions, of the oxidative processes, and in the end a variation in the rate of new formation and growth of the very tissue that has functioned. This is not the whole story in the living animal. After the functional act of energy liberation, the chemical by-products diffuse into other parts of the body, or are carried by the circulation, and thereby become secondary factors in stimulating or restraining activity and growth in such parts. These effects are like an endless chain and are cyclic. In fact chemical products of physiological activity constantly influence the development and growth of all parts of the individual body.

The physiological interrelationships within the body of the human are also infinitely complicated and more or less cyclic. The processes of activity occurring in certain parts or organs of the body are constantly conditioned by what occurs in other organs or parts. Such influences are of two great physiological classes, (1) augmentative or *stimulative*, and (2) retarding or *inhibitive*. These are illustrated by well-known physiological processes such as the control of the heart rate, or the associated inhibition and stimulation of antagonistic muscles, by the stimulation and inhibition of the motility of the stomach, etc. We know the details and the extent of inhibition and the external expression of it in organs, but physiological science has yet conclusively to explain just how such restraint is accomplished.

Analogies are to be had also from the plant world. Dr.

Hooker's[1] study of the cycles of growth, rest, and fruition in plants is a most notable recent contribution to this field. He has found that the stages of rapid growth in fruit trees, with the extensive development of the chlorophyllic and photogenic apparatus which produces and stores carbohydrates, slows down in activity as carbohydrate accumulates in the storage reservoirs. In other words the development and presence of the end products of the activity of the photogenic apparatus are inhibitive and restraining to these processes. This may even go so far as to lead to the destruction of the photogenic apparatus itself. The presence of an excess of stored carbohydrates, on the other hand, is favorable to the development of the carbohydrate-consuming apparatus represented in the flowering and fruiting mechanisms. When the carbohydrates are exhausted, then the photogenic apparatus becomes more active again. This brief mention suggests that inhibitions and stimulations to growth of the photogenic apparatus affect the growth and development of the fruiting apparatus, but the influences operate in inverse ratios. Physical and chemical laws are undoubtedly at the bottom of the processes, just as in animal development. Certain processes favor inhibition of growth and development, while others favor stimulation of growth and development.

For example, activity of muscle is stimulated or inhibited by activity in nerve; or activity in nerve may be augmented or retarded by activity in gland. The principle is the same whether activity is measured by functional energy manifestation or by mass change expressed in growth. It is far more important to recognize that the conditioning factors in a complex plant, or in an animal like man, are legion, and that they are balanced in algebraic sums of positive and negative influences. Many of these factors are known, but apparently many more are unknown at the present time. These are some of the content of the phrase "the growth impulse."

If one studies the phenomena of growth from the standpoint of the size and mass of the individual animal and the time in-

volved in development, as was presented in detail by Professor Brody in the second lecture of this series, he arrives at certain mathematical curves and graphs expressing the relations between these factors and the time of the life cycle. For example, in the rat, in the ox, in the human, the growth curve is characteristic and in most respects very similar. It begins at a certain rate of acceleration, passes through the major part of a growing cycle at a definite rate, and as age approaches that rate slows down to a level of no addition to the mass, that is, no growth. Growth in this sense is a function of time and mass. Height or breadth, or any linear dimension can be taken and by application of the formulae the growth curves can be constructed.

Another point of view was emphasized by Dr. Jackson, namely, that growth in mass of the whole animal is the sum of the growth of the parts. He gave evidence to show that the rate of growth in mass of the individual parts of the animal body, when expressed in the form of curves, shows phases of acceleration and of retardation of growth at different periods in the life cycle. The periods of maximal growth do not coincide for the different organs. There is in the anatomical museum at McAlester Hall a series of models of human embryos of different ages constructed by Dr. Jackson and his students, in which the body trunk of each embryo is reconstructed on a scale of magnification to enlarge it to the length equivalent to that of an adult. These models are a striking illustration of the fact that the relative size and rate of growth of the vital organs varies extremely at different ages. In the very early embryo the heart and the brain are relatively very much larger than they are in the adult. Examining a series of models representing as many ages one cannot escape the conclusion that the heart grows extremely rapidly in the early embryo. Later, as the size of the body as a whole becomes larger, the heart is ever relatively smaller and smaller. Of course the heart actually continues to grow in volume, but at a very much reduced rate. A similar comparison may be made with reference to the brain. The brain

and embryonic nervous system is one of the first differentiations to occur. It quickly attains a mass representing a high per cent of the total volume of tissue in the embryo. The rate of growth of the brain tissue and the degree of differentiation in growth of nerve cells is enormously accelerated in the human during the first nine months of embryonic life. In fact it is the general belief at the present time that few if any new nerve cells are formed after birth. The nerve cells continue to grow in volume and length of processes throughout childhood and adolescence, but they do not form new cellular units.

Another internal organ offers a striking illustration in this respect, namely, the liver. The liver originates as an outgrowth of the embryonic alimentary tube. It is not recognizable until a somewhat advanced stage in embryonic differentiation. However, the embryonic liver tissue grows so rapidly that it represents a large proportion of the total body mass at a late embryonic and prenatal stage. In postnatal development the growth of the liver is ever at a relatively much slower rate. Compared with the heart the liver is much later to appear in the cycle of embryonic development. It reaches a maximum rate of growth before birth, and grows at a slower and less prominent rate during childhood and early adult life.

It is obvious that certain outstanding physiological factors are operating in the human body and in the body of animals to control or regulate, or at least to influence the rate of growth, and that these influences do not affect all parts of the body in the same degree at the same time.

Furthermore, it must be recognized that the growth-influencing factors operate more and more on individual organs and tissues and each influence is intensified at different times in the developmental cycle. At times the algebraic result is a physical body quite out of all proportion to the average size and body form which we ordinarily recognize as normal. Such individuals are expressions of growth abnormalities and yet they are only extreme variants.

Perhaps a further illustration from the physiology of an adult animal would serve to clarify the functional interdependence of organs which has been discussed. The illustration applies to man, but the facts have been developed in the study of rabbits, dogs, and man.

There is a widespread common knowledge of the nervous system and its normal functions, of the physiology of the liver, of the pancreas and its digestive functions, and of the physical nature, the chemistry, and the physiology of the blood. Perhaps you remember that in the blood there is a very constant amount of sugar, varying only slightly from 0.12 per cent from hour to hour throughout the day. Among other great functions the liver always contains an excess of stored sugar in the form of glycogen. During the absorption of a meal the sugar principles are entering the blood stream in greater amount than normal to the blood and are rapidly abstracted, polymerized, and deposited in the liver as glycogen. During fasting, when no sugars are absorbed from foods, the liver glycogen is slowly redissolved and reënters the blood stream at a rate just adequate to keep up a constant blood sugar.

The nervous and muscular tissues consume these sugars, and their normal behavior absolutely depends on the constancy of the sugar supply. It is not so generally known that the pancreatic gland, which is so important for the digestion of food, is of very great importance in that it produces a group of chemicals which also enter the blood and which are absolutely essential to enable the body to use its sugars. If the pancreas is surgically removed from an animal, or destroyed by disease in man, then sugars cannot be used by the muscles and the nervous system, the animal quickly often in a few hours becomes unconscious, has nervous-muscular convulsions and promptly dies. The animal cannot utilize the sugar present in abundance without the internal secretion of the pancreas.

If, on the other hand, the liver is removed from an animal, thus taking away the stored source of sugars so that no sugar

can be formed and diverted to the blood stream, then the sugar present in the blood is quickly oxidized and disappears and the animal becomes unconscious and dies as before. The truth of these facts is based on numerous experiments in which the artificial supply of pancreatic secretion is furnished,[2] or artificial sugars are injected into the circulation.[3] Either step is promptly followed by temporary recovery and normal behavior. The interdependence of the nervous system, the muscles, the pancreas and the liver, and other adult organs of the body, largely chemical in the illustration used, is obviously essential to the continued activity and normal growth of man and mammals.

The growth-influencing factors include not only that protoplasmic complex of inheritance which we describe by the phrase "the growth impulse," but they include the physical and chemical processes going on in every individual part of the body at every moment whereby that part exerts directly or indirectly either a stimulating or a restraining influence on other parts of the individual.

One may summarize for emphasis the general facts described in this introduction. They are: (1) growth during the life cycle of individual animals proceeds[2] according to a certain mass-time ratio expressed by the curve of growth. (2) Growth of the individual parts of the animal occurs at very decidedly different rates than the average growth as a whole. (3) The maximum rate of growth in different organs is reached at different times in the life cycle. (4) Growth rate and growth volume and differentiation within the body are conditioned first of all by the unknown capacity of the protoplasm expressed by the phrase "the growth impulse." These factors are inherent but vary widely in different species. (5) Coincident with the morphological differentiation of parts of the body of animals and of man, there is a functional differentiation equally intricate and diverse. (6) It is a law of physiology that the functional act in the tissue or group of tissues stimulates the rate of growth in that tissue. This influence apparently has a chemical or

physico-chemical basis. (7) Every organ or special tissue, by virtue of its physiological activity, produces chemical by-products which, when distributed throughout the body of an animal or plant, exert a definite influence on the rate of growth, development, and activity of all other parts. (8) These inter-organ reactions are infinite in variety, but are broadly of two classes, namely, those which stimulate or augment reactions and those that inhibit reactions. Not only the growth in mass but the growth and development of activity in the parts of the animal are conditioned by the physiological factors expressed in this interaction of the parts of an animal or plants. (9) Extreme over- or underproduction of special substances elaborated by the organs of the body itself may stimulate or retard growth to such an extent as to produce extreme deviation from the average normal, *i.e.*, abnormal body form, undersized pigmies, and overgrowth or giants.

I. The Hormones

In mammals and the higher vertebrates the chief chemicals that control the growth processes of rate, volume, and the growth time cycle to so great a degree have developed into special substances produced by special organs within the differentiating body itself. These substances as a class received the name of "hormones" by Starling[4] in 1912. They are present only in minute amounts and exert influence only after distribution through the circulatory system to all growing structures. It is this class of substance such as that produced by the pancreas in the illustration already used, that we wish especially to emphasize.

In discussing the influence of hormones one must recognize that the usual studies of growth and the growth curves assume average standard conditions. In other words, the human growth curve shown by Professor Brody is a curve of the standard average growth of the human as a type. All the factors that I am emphasizing are theoretically acting normally, and to that ex-

tent are taken into consideration in the establishment of average growths.

It is only by the extraordinary action of the hormones in individual cases in which variations from the normal type occur that we secure the knowledge from which we are able to deduce the function of each individual hormone. It is easy to understand that the study of abnormalities of growth is largely the study of individuals of extreme variation from type.

In mammals and the higher vertebrates the hormonal mechanisms for the control of growth processes have evolved much further than the secondary and casual impress of the chemical waste products of the processes in other organs or parts. Hormones may, therefore, be defined as particular chemical substances produced in certain tissues of man and animals which have become differentiated in such a way as to exert a degree of chemical control of other organs through an adaptation of the one to the other. Hormones occur in minute amounts only. The origin and significance of the more important hormones will be briefly discussed.

II. The Hormones of the Thyroid

Everyone is familiar with the gland of the neck known as the thyroid, and its excessive overgrowth called goiter. Certain regions of the United States are known as goiter territory because of the high prevalence of disturbed development from abnormal functioning of this gland.

There are two types of thyroid disturbances which produce a profound influence on growth. These are known physiologically as hyper- and hypothyroidism and follow in train with corresponding changes in function of the thyroid gland. The hyperthyroid individual is characterized by spareness of body, underweight, by excessive muscular energy, by aggressiveness, by nervousness, and by extreme irritability. If we physiologically analyze further we find a high heart rate, excessive blood pressure, overactive motility of the alimentary canal, and, most

striking of all, an excessive heat production which often manifests a definite hyperpyrexia. The whole picture is that of an excessive drive of metabolism. The rate of oxidation, that is the measure of metabolism, may be increased to 20, 50, or even 100 per cent above the normal. In the milder stages of hyperthy-

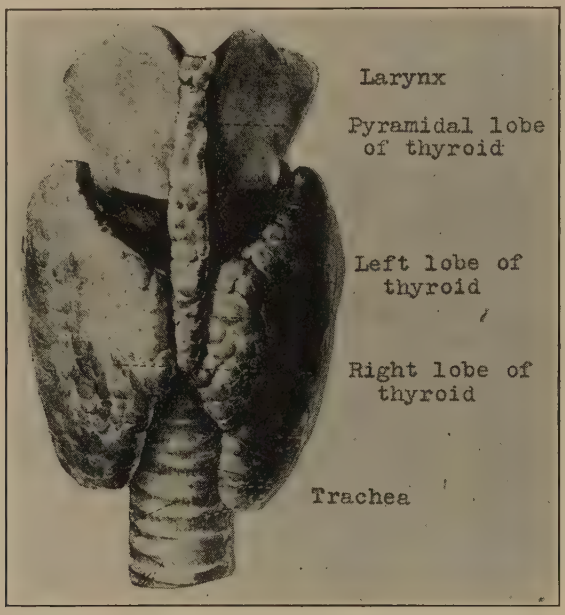


Figure 77. The thyroid gland of man showing its form, size, and location. After Spalteholz. *Hand Atlas of Human Anatomy.* By permission of Verlag S. Hirzel, Leipzig.

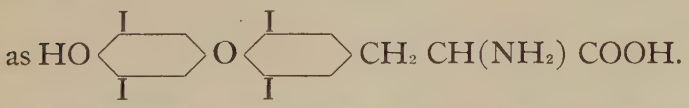
roidism such persons are often the aggressive, energetic business men, the social reformers, and at times the unbalanced fanatics. Physiologically they lead a more active life and at a faster pace. They quickly run their course, generally to an extreme pathology unless aided medically.

Hyperthyroidism is due to an excessive production of an active hormone. The hormone is discharged from the gland follicles into the blood stream, through which it reaches all parts of the body. Its amount depends not so much on the size of the

gland as on the greater rate of functional activity. This hormone is an iodin compound of an amino acid. It was chemically isolated and identified by Kendall[5] in 1915, who named the

Figure 78. Typical appearance of untreated cretin, hypothyroidism of infancy. From *Diseases of Infancy and Childhood* by Drs. Holt and Howland. Courtesy of D. Appleton and Company, New York.

substance *thyroxin*. It contains as much as 63 per cent of iodin. Harington[6] has recently determined the correct clinical formula



The thyroid hormone accomplishes its accelerating influence on physiological processes through direct stimulating action on

the rate of metabolism of all tissue protoplasm. In fact it is explained as a deamidizing agent that hastens the liberation and destruction of amino acids and their excretion by the body. The acceleration of oxidative and catabolic processes may sharply distort the normal average body growth and form.

Underdevelopment and hypoactivity of the thyroid is expressed in a very different but characteristic way on the growth of certain tissues. Infantile hypothyroidism stunts growth in size and stature, producing cretinism. A cretin is a dwarf for his age. His skeletal and connective tissues do not grow in normal rate. There is a marked increase in the relative mass of subdermal connective tissues. The abdomen is protruding. There is a fullness of face, lips, nose, thicker skin, and enlarged tongue which in the extreme case overfills the mouth. The eyes are peculiar and expressionless, the reactions of the nervous system are sluggish and imbecile in type. In short, the appearance of the ordinary cretin is that of a dwarf with low mentality.

Figure 79. Artificial cretinism in the sheep induced by surgical removal of the thyroid glands in a lamb aged two months. The figure shows the animal at fourteen months of age in comparison with the sheep of normal size. After Sutherland Simpson. By permission of the *Quarterly Journal of Physiology*.

That the cause of cretinism is due to absence of the thyroid hormone is best shown by the effect of artificial thyroid feeding. After a few months of thyroid feeding the skin of a cretin clears and becomes thinner and more normal in texture, the eyelids are thinner, the lips and tongue smaller, the activity and expressions more alert. Skeletal growth is again accelerated. The imbecile cretin is transformed to the alert normal child. This defect of the thyroid when congenital is probably never

remedied by later growth of the gland, but fortunately, artificial medication can be continued indefinitely.

Experimental cretinism results when the thyroid gland is surgically removed in young animals. Figure 79 shows a cretin sheep produced by Dr. Sutherland Simpson[7] by removing the thyroid gland from two-months-old lamb. In comparison with the adult sheep these cretins were "squat and stunted in growth, with misshapen rickety limbs, and the general appearance was listless and stupid." The wool was coarse and rough and the body temperature was lower than that of the normal sheep. All these factors compare very well with observations on the human cretin.

Figure 80. A case due to hypothyroidism or myxedema occurring in adult life. The club-shaped fingers, heavy features, and the listlessness of the eyes and facial expression are characteristic. From Tigerstedt's *Textbook of Physiology* by R. Tigerstedt and John R. Murlin. By permission of D. Appleton and Company, New York.

Hypothyroidism of later life of the human produces a picture of the body also very characteristic. There are many such unfortunates, especially among women in whom the condition appears at the age of forty-five or fifty, or even later. These abnormal types are called myxedemas. They have full round faces, thick, heavy but firm skin, heavy, clubbed hands and fingers, thick cheeks, lips, nose, and eyelids, they are nervous but inactive, lethargic, listless, and dispirited. The optimistic and aggressive reactions of the normal human are produced by the simple method of feeding the proper amount of artificially prepared desiccated thyroid gland containing the hormone. Fortunately, thyroid gland itself can be taken as food without the necessity of extracting the pure hormone, and it seems to produce in the body the good effects that come from normal production of the thyroid.

III. The Parathyroids

In the human there are four tiny glands called the *parathyroids* which lie on the surface, or slightly imbedded in the surface of the thyroid. Each of these is not more than three or four mm. in diameter, yet the presence and normal function of these glands is necessary to the growth and development

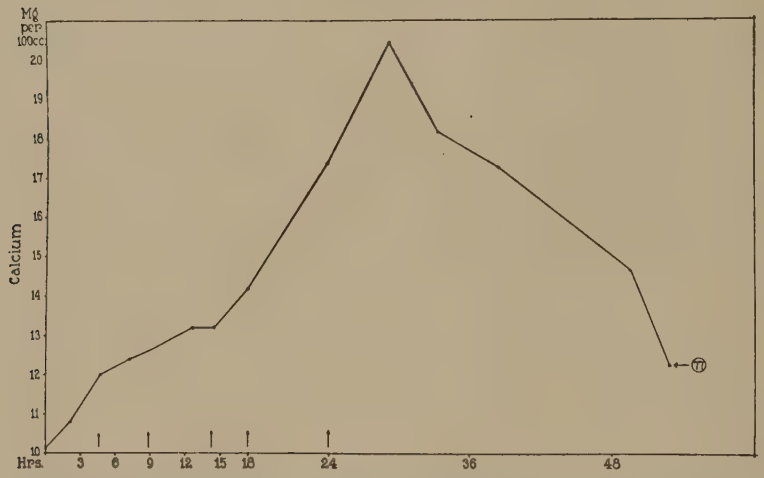


Figure 81. Curve showing the increase in the calcium content of the blood due to injections of parathyroid extract at intervals indicated by the arrows. Clark, Collip, and Scott. Permission of the *Journal of Biological Chemistry*.

of the individual. If they are surgically removed in animals or man or undergo degeneration from X-ray or other treatment then a train of nervous symptoms with severe cramps, muscular twitchings, and tetany follows. These attacks may and in general do end in asphyxiation and death.

Collip[8] has prepared a purified extract of the parathyroids which when given to experimental animals with or without parathyroids greatly increases the amount of calcium in solution in the blood. When the glands are entirely removed, the calcium content drops below normal to 3 or 4 mg. per cent as compared with the normal calcium of 8 to 10 mg. per 100 cc.

of blood. The hormone produced by the parathyroids influences growth and activity by controlling the amount of available calcium in the blood. Calcium in turn is absolutely necessary to numerous protoplasmic reactions, including the development of normal nerve reflexes, normal muscular contractions, heart beats, etc. This hormone is necessary for the control and regulation of very special chemical reactions of vital necessity to metabolic processes of growth and energy transformation.

IV. The Hormones of the Suprarenal Glands

The pair of small glands in the abdominal cavity lying somewhat above the kidney, like the thyroid gland, produce internal secretions that seem necessary for continued life. Whenever the entire suprarenal is removed surgically, definite functional changes take place that terminate in death in from one to five or six days. Addison's disease, first described in 1849, is known to be due to disease and impaired function of these structures.

The suprarenal is derived from two embryologically distinct sources. The cortex comes from the embryonic mesoblastic tissue in close relation to the reproductive ridge, while the medulla arises from neuro-epithelium and is related in origin to the sympathetic ganglia. An active substance *suprarenin* has been isolated from the medulla, but not from the cortex. This medullary hormone has been identified chemically by Abel,[9] Aldrich,[10] and Takamine.[11] It has the following structural formula:

This amino derivative has been produced synthetically and the synthetic product influences the organs of the body in a way comparable to the natural product. Epinephrin and thyroxin are the only hormones whose chemical identity is now known.

No active hormone has been derived from the cortex, though it is believed that such exists. Further, it is the loss of the cor-

tex, or its experimental hypofunction, as we at present believe, which leads to the death of the animal. But clinical and pathological evidence, especially the presence of tumors of the adrenal cortex, indicate that overgrowth of the cortex is associated with the overdevelopment and character of the secondary sexual growths. The masculine or feminine features, the beard and growths of hair on the body are all expressions of form depending in part on the amount of secretion of the adrenal cortex. The evidence is derived from cases of overgrowth of this organ. The condition of virilism, Figure 82, has been associated in numerous instances with the presence of tumors of the suprarenal cortex and the corresponding overfunction. Surgical removal of the tumor is followed, as in the case figured, by slow return to the feminine features, loss of the beard and recovery of normal feminine functions.

We know in detail what the hormone from the adrenal medulla does in terms of physiological reaction. It stimulates an increase in function of all those nervous mechanisms which we call the sympathetic autonomics. Of course this is a technical explanation, but everyone can realize that under certain conditions the heart rate is enormously increased, that the size of the small blood vessels may be increased or decreased as in blushing or in sudden pallor, and that the motility of the stomach and intestinal tube under certain conditions seems to be augmented, or relaxed beyond all normal limits, that the pupil of the eye is widely dilated, or that the hairs "stand on end." These are illustrative of the control by the sympathetic nervous system of physiological conditions. We call these reactions autonomic because we have absolutely no individual voluntary control over them. We are often conscious of the fact that they are operating but we cannot by any conscious effort change the reactions as we do those of our skeletal muscles. The active principle of the suprarenal gland acts as a chemical whip on all such nervous complexes. For example, the heart rate is accelerated and its volume increased, the vasomotor tone is maintained, the reac-

tions in the alimentary tract are kept on a normal level, and the rate of secretion of the hormones of the thyroid and of the suprarenal itself are regulated and controlled, because the epinephrine specifically stimulates the nerve endings of the thoracic sympathetics wherever they may be found. It raises blood pressure, favors sugar metabolism, and Boothby[12] has shown that it has a specific dynamic action in raising the rate of metabolism. It does not take extreme scientific training to appreciate that such physiological reactions are at the very foundation of activity, nutrition, and growth. The point is that the suprarenal hormone operates so subtly that we cannot always point with certainty to the exact part it plays in the process. We again emphasize that the study of growth by mass measurements or by any other method must take into account the factors which influence the details of the functional process, hence the growth processes.

Figure 82. Masculine form of a woman due to a tumor which increased the secretion of the cortex of the suprarenal gland. After surgical removal of the tumor the beard was lost and the form slowly returned to the feminine type. From Gould and Pyle's *Anomalies and Curiosities of Medicine*. By permission of W. B. Saunders Company, Philadelphia.

V. The Hormones of the Reproductive Gonads

The interstitial tissues of the reproductive gonads, the corpus luteum and follicles of the ovary, and the placental membranes all yield growth-stimulating substances. The best known of these are from the female ovary. It has long been known that domestic animals and the human do not develop the characteristic body type of either the male or female of the species until the sex gonads are mature, and that certain parts of the reproductive system atrophy on removing the gonads. It was only in 1900 that Knauer first proved that these atrophies failed in

part on transplanting living ovaries. In 1912 the first purified alcoholic extract of ovarian tissue was proven to have an influence on those growths of reproductive tissue associated in the oestrous cycle in mammals.

Hermann and Fränkel[13] in 1915 perfected methods for preparing and purifying an active ovarian extract. This preparation injected into females actively stimulated growth of parts of the uterus, the uterine tubes, and other structures of the reproductive system. It also stimulated premature sexual growth in immature animals, and induced the physiological phenomena of oestrus.

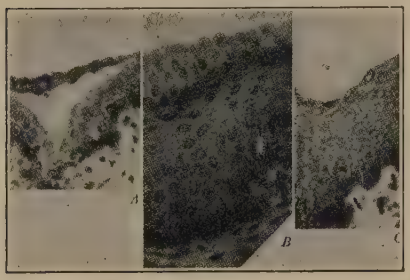


Figure 83. The effect of artificial injections of ovarian hormone in stimulating growth of the lining membranes of the female reproductive system in spayed rats. (A) Epithelium of the uterus of the control rat. (B) The same thirty-six hours after injecting hormone. (C) Forty-eight hours after injecting hormone. After Allen. By permission of the *Journal of the American Medical Association.*

Dr. Edgar Allen, my colleague of the Department of Anatomy, of the University of Missouri, collaborating with Dr. E. A. Doisy of St. Louis University, in 1923[14] began publication of their numerous investigations on this subject. They quickly demonstrated an active *follicular hormone* present in the follicular fluid of the pig's ovary. This they purified and tested by the latest physiological and morphological methods. They did not find the substance in the corpus luteum of the pig. But Allen has now shown that it is present in the follicles from a variety of animals, including the pig, cow, sheep, hen, and human.

Allen[14] has clearly demonstrated that this hormone is responsible for stimulating the definite growth cycles in particular tissues of the female reproductive organs. The walls and lining membranes of the uterus and vagina hypertrophy when the follicular extract is injected into the body. The hormone is distributed by the circulation, stimulates a growth cycle in the epi-

dermal tissues, the muscular and supporting tissues, and in the vascular supply of the vaginal and uterine walls, and in the mammary glands.

The changes in rats and monkeys are accompanied by all the phenomena of oestrus, and are accomplished within a time interval equivalent to that of the oestrus of the normal animal. The growths can be induced in female rats at an age many days earlier than that of the normal puberty, or in rats or monkeys that have had the ovaries removed, in which normal oestrus no longer occurs.

When injections of the artificially prepared hormone are stopped, overgrowth ceases and a degree of degeneration occurs. This type of overgrowth and its following retrogression are characteristic of the preliminary stages in the reproductive cycle in all mammals. It is, in fact, the structural basis of the oestrous cycle. This is indeed a highly specialized type of growth-producing influence, nevertheless, it is of most vital importance in the physiological economics of the propagation of the mammalian species. The unique and classic contribution of Allen and Doisy consists in reducing the oestrous phenomenon to a definite causative basis, in demonstrating that a single hormone, abundant in the ovarian follicle, is the essential causative factor in the cylic oestrus and menstrual changes in the maturing female.

The later publications of Allen and his colleagues establish the presence of this reproductive hormone in many other tissues,—the corpus luteum in the human, the growth which fills the cavity of the follicle when the ovum is discharged, the placental and fetal membranes of the human, the bovine, and other mammals. It is evident that the follicular hormone plays a very essential part in the growths and maturity of the body during adolescence, and in particular during the succeeding active reproductive years. It is also evident that the atrophic changes in the organs of the reproductive apparatus and the deviations from type in the growth and development of the

asexual types, are explained by the absence of the reproductive hormones.

An example of an extraordinary growth stimulation followed by abrupt inhibition and atrophy of particular reproductive tissues may be mentioned at this point. During childbearing there is an excessive growth of the muscle of the walls of the uterus. The total mass increases several hundred per cent above the normal size of the resting organ. Immediately following birth this tissue stops growing and rapidly retrogresses. Within a few days it is resorbed and returns to approximately the normal size. The whole cycle of growth and rapid decline is primarily dependent upon the presence or absence of particular but unidentified hormones. The facts are not so clearly determined, but possibly it is a part of the same process that the chorionic villi and placental membranes of the embryo grow into the lining membranes of the uterus forming a very elaborate nutritional apparatus of blood vessels and blood channels, with a very considerable amount of new tissue. At birth this growth usually ceases, the excessive chorionic mass also retrogresses, and the placental tissues are shed. The process is almost miraculous in its efficiency. Occasionally, however, bits of these chorionic tissues, which by the rule ought to degenerate and disappear, in fact continue to grow without check. They become cancerous in fact. Fragments may be displaced and grow parasitic in new positions. In the end they destroy the life of the unfortunate victim. Obviously some chemical factor in the inhibitory control of the embryonic membranes has failed with disastrous and fatal results.

VI. The Pituitary Gland

Always among large groups of human beings one finds an occasional man or woman of unusual height and size. The ordinary height of normal adults is between 5 feet 4 inches and 6 feet. In every selected group of young men, as, for example, in the student cadet battalions of the University, we are impressed

by the fine height and straight bearing of Missouri men. Yet, several hundred students, classified on the basis of graded height, seldom deviate outside the above limits. Any marked deviation above this average in height may be classified as *gigantism*, and a pronounced variation in the opposite direction would be classified as *dwarfism*.

In America there are many extreme cases of gigantism, as an example, the "Denver giant" over 8 feet 10 inches in height, or the Texas lad mentioned in the recent daily press who writes me that he is 8 feet 1 inch tall and weighs 300 pounds at the age of 19. These excessive heights are abnormal and are due to very definite causes.

Gigantism is primarily a defective or abnormal overgrowth of the skeleton, in particular the long bones of the legs, arms, hands, feet, etc. The long bones grow from three ossification centers. One for each end, the epiphyses, and one for the shaft, the diaphysis. When these centers of bone development fuse then growth in length of the bone ceases.

Excessive skeletal growth occurs in response to the overstimulation by substances produced in the anterior lobe of the tiny gland at the base of the brain known as the pituitary. This gland when overactive stimulates excessive growth of bone and connective tissues, when underactive it retards growth and the individual is small and infantile in appearance. The physiological activity of the pituitary gland may under some conditions be greatly accelerated. At such times it produces a greater quantity of its secretion or hormone and this overstimulates the growth processes in the skeleton.

Causes of hypertrophy of the pituitary are not so readily determined, but the effects on size and stature are clear cut and distinct. In giants, an increase in function of the pituitary has occurred at an early age, *i.e.*, before the union of the three growing centers of the long bones. The universal history of extreme gigantism is that the excessive height was first observed in early youth more often between the ages of 12 and 18, sel-

dom later. Professor Brody has shown that the period of adolescent growth in the human is coincident with rapid growth. The pituitary is more active during this age. We can scarcely escape the conclusions, that gigantism is overgrowth induced under the stimulating control of the hormones of the pituitary.

There is another type of abnormal and excessive growth, a type which begins in adulthood when a man has passed the normal span of years of active growth in stature. The long bones do not take much part in this form of the growth, but the bones of the skull, cheeks, jaw and face, and chest are strongly affected, producing great enlargement, this change in the head is known as *acromegalia*. As early as 1886 Marie associated this growth with disease of the pituitary. Cushing's[16] operative and experimental work (1909) has become classic. Cushing records a series of pictures of a young man who at about the age of 25 first noticed an increase in the size of his head and facial outlines. At the age of 40 the facial features were coarse, heavy, and excessively overgrown. Mild examples are more or less common among persons from 35 to 50 years of age. Gigantism and acromegaly are examples of stimulation to growth by overactivity of the pituitary by the anterior pituitary hormones. These are clear cases of hyperpituitaryism.

Cushing operated the anterior pituitary lobe in young dogs and noted that these failed of full development and remained infantile. He transplanted anterior lobe with demonstrated improvement in growth. Long and Evans,[17] proceeding on the known fact that transplanted tissues are resorbed, prepared suspensions of finely divided anterior lobe which they repeatedly injected into the peritoneal cavity of growing young rats. They obtained giants of double the size of normal litter mates.

That this lobe influences growth of other than skeletal tissues has just been brilliantly demonstrated by Smith and Engle.[18] It has long been known that certain endocrine glands have a functional interdependence. For example, the relative size of the pituitary, the thyroid, and the suprarenal varies each

according to the degree of injury, or intensity of function of the other. It has been argued that the influence is reciprocal.

Furthermore, each of these glands influences the gonads. Smith and Engle by repeated transplants of anterior pituitary gland tissue into the muscles of young mice induced not only precocious development of the oestrus but a pronounced overgrowth of the gonads. The mass of the ovaries of mice were as much as nineteen times and rats ten times those of untreated litter mates. Furthermore, "superovulation, or the liberation of an unusual number of ova invariably occurs." They found "forty-eight apparently normal ova in one tube in a twenty-day-old mouse, and in a twenty-six-day old rat." Young rats mature at about forty to sixty or more days of age. The transplanted tissue contains a hormone which stimulates the development of the follicles, bringing more embryonic follicles and ova to full maturity. In the absence of the anterior pituitary hormone the gonads degenerate. When it is supplied again they grow and normal functions are reëstablished.

Dwarfism on the other hand and the persistence of infantilism beyond the usual age of puberty in the human are examples of anterior pituitary inactivity, namely, lack of pituitary hormone formation or *hypopituitaryism*. Both pituitary lobes are often involved. A failure of the normal growth of the pituitary and of the normal amount of secretion of the pituitary occurring in early childhood, is accompanied by failure of the usual rapid growth in height and weight characteristic of the age of puberty in both boys and girls. The skeleton does not grow to its full capacity, the muscles do not develop to the usual extent, the skin remains childlike in texture, and the facial features, the beard, and other external changes characteristic of adolescence are absent, and the external genital organs remain childlike and infantile. There is often a peculiarly excessive deposit of fat so that these cases are overweight for their height. Hypopituitaryism may occur after adulthood is reached, due to causes unknown. The picture, however, is clear cut and characteristic.

An adult afflicted with posterior lobe hypopituitaryism is tolerant to sugars. He produces an excess of fats which are deposited in large amounts subdermally in special regions of the body, which actually distort his proportions. Great aprons of fat occur on the chest and abdomen and to a lesser extent on the hips and legs. Extreme cases look like monsters.

It is not desirable to discuss the matter in too great detail but it gives some idea of the difficulties the physiologist must surmount in experimental testing to remember the location and structures of the pituitary organ. This small endocrine gland in the human is a mass less than one cubic centimeter in volume and weighs only 0.6 of a gram. It is richly supplied with blood vessels. Embryologically the pituitary consists of two lobes or parts. The posterior lobe grows from embryonic brain tissue, the anterior lobe is from the tissue that gives rise to the walls of the mouth and pharynx. It is the anterior part that produces the hormone which induces gigantism, while the posterior part interferes in part with the chemical fate of and increases the tolerance for sugars expressed by an enormous sugar appetite.

Very active preparations of extracts of the posterior pituitary lobe have been produced and have been listed among commercial drugs for some years under the name of *pituitrin*. Dr. Abel[19] of Johns Hopkins University has contributed most toward the identification of the posterior pituitary lobe hormone. He classes this substance as an amino acid derivative, a histamine-like body. Recently he isolated a *pituitary tartrate* so intense in action that it produces a measurable physiological change in dilutions of one part in 18,750,000,000. This is equivalent to 1 gram dissolved in 18,750,000 liters of water, a volume not less than 50 times the total capacity of this (the Physics) lecture room. This is the most vigorously active physiological substance known at the present time.

The facts presented in the preceding discussion are largely those observed in the human. They are confirmed and extended by experimental observations on lower animals. Both the human

data and the experimental data indicate that growth is influenced by the two main divisions of the pituitary gland in very distinctive ways. Furthermore, the influence of each gland is expressed in a twofold way—that produced by oversecretion, or hyperactivity, and the condition induced by an undersecretion, or hypoactivity. There is not complete agreement among the investigators of the pituitary, but, summarizing and combining these sources of information, it would seem that the anterior lobe in hyperactivity stimulates excessive growth in man and lower animals. Rats grow to double their normal weight and man to giant stature and giant weight. The muscular system of animals and man is overdeveloped. The growth of the ovaries is excessive and superovulation and the oestrus are facilitated. Hypoactivity of the anterior lobe retards skeletal development, the muscular system is small and weak, the development of the nervous system is retarded, and mentality is subnormal. Metabolism is definitely reduced and the temperature is lower than normal. In the posterior lobe an increase in activity augments sugar metabolism, stimulates the contractions of smooth muscle in the intestine, reproductive system, and blood vessels, and produces hyperirritability. A deficient posterior secretion is characterized by decreased oxidation, increased volume of urine, carbohydrate tolerance with excessive fat production, nervous or mental indolence and inactivity, abnormal body form, and infantilism.

VII. The Influence of Physiological Exercise on Growth

A further important physiological point of view was expressed by Dr. Robbins in the introductory lecture of this series, namely, that growth processes are inseparable from dynamic processes. Energy liberation is ever accompanied by destruction and repair of body tissue. Growth in animals is not a simple accumulation of a mass of stored materials, it is the formation of a mass of intimately organized and highly differentiated living protoplasm of corresponding complex physiological capacity. A

close analysis reveals that physiological activity destroys protoplasm. The fatigue of an athletic contest, or of a day's labor in the shop or the fields, is for the moment destructive of growth. Often more tissue is destroyed than is rebuilt after the activity occurs. The question then, may well be raised, what is the true relation of activity to growth.

We have already expressed the law that physiological activity of living protoplasm favors its further growth and development. The very act of protoplasm necessary to liberate energy stimulates the complex processes of metabolism which later produce further growth of the tissue reacting. This is the chief underlying principle of physical training. But like all such so-called laws of biology the law holds true only within a limited range of activity. That range cannot be expressed in general terms but must be determined both as to intensity and as to duration of activity in adaptation to the physical capacity of each individual.

Reactions to short and intensive physical effort are coextensive with the reactions of the different physiological systems of the body. The respiratory, circulatory, cutaneous, nervous, muscular, alimentary, and endocrine systems all take part. Each of these responds by more intensive catabolic changes and augmented energy output. In the after-period the "compensatory reactions," or augmented activities, continue for a time and metabolism is correspondingly favored. Not only will there be full repair but growth will be actually accelerated. This is the true stimulating effect of exercise. The beneficial effects extend throughout the body. The muscles are stronger and larger, the nerve reactions are more vigorous, secretions are better, the circulation is more tonic and the heart stronger, nutrition is accelerated and growth is stimulated. These responses are more delicately balanced in the young. It must be the keen insight of the trained arbiter of our athletic activities that determines the intensity, the duration, the repetitions, and the correlations with age with the degree of strength and development already es-

tablished if the optimal physiological responses are to be attained.

Inactivity deprives the body of this stimulus to development. Overactivity produces extreme fatigue and exhaustion for which the compensatory reactions are inadequate. Metabolism is not accelerated but is retarded. Positive injury results. Growth is delayed and the body is stunted. The effects are more deeply seated than a simple reversal of ledger balance between food consumptions and growth, as against energy liberation and tissue destruction. The overwork in some way injures the body protoplasm and the result is expressed in inertia, atonia, and retarded metabolism. These extreme results are, of course, outside the law that adjusted functional, that is, physiological activity, begets energy, endurance, and growth.

VIII. Pathological Tumors and Cancerous Growths

There are numerous tissues throughout the body, especially epidermal, muscular, glandular, and connective tissues, which may run riot in growth, forming masses that are abnormal in size and in function. These extra growths in turn produce physiological substances not normal to the body but which may be toxic and destructive. One may emphasize in these instances the failure of inhibition or restraint of growth process to the ordinary average level described as normal.

The subject of abnormal growth and abnormal activity looms large in the great field of pathological physiology. Perversions of mass development and of the functional capacity may occur in almost every part of the body and under an almost infinite variety of conditions, many of which are quite unknown in their causal relations. These growths and growth perversions call for consideration, though the subject cannot be treated here with any degree of thoroughness.

In this field belong the great variety of special growths or tumors, both benign and malignant. These structures are atypical and abnormal, both from the standpoint of orderly growth of

the body as a whole and from that of the differentiation of its parts. At the present time such growths are viewed as cellular perversions. They are masses of cells and tissues, or combinations of tissues arranged in abnormal fashion and developed in abnormal amount. They do not serve the normal functions of the body and are in the end more or less destructive to the life of other normal tissues. The growth of tumors in general is progressive, rapid, and may be destructive to the host. They infiltrate into parts of the body otherwise normal, and in the very process of their growth interfere with the nutrition and growth of normal parts.

Abnormal growths of pathological type have been classified on many bases. Perhaps the most satisfactory is the grouping according to the type of tissue from which they have been derived and which they resemble. Almost every tissue in the body may give rise to tumor growths. The supporting tissues of bone, cartilage, connective tissue, lipoid tissue, lymphatic, blood vascular, all may give rise to special growths. These are called osteomas, chondromas, fibromas, lipomas, angiomas, etc. Or, perverted growths may develop from muscles—either smooth muscle or striated, from nervous tissues—either ganglionic, supporting, or of epithelial type, or they may be derived from gland, or pavement epithelium, or epidermis.

Certain of these perverted growths seem to be little more than hypertrophy of otherwise normal structures. Such growths are highly vascular and more or less benign. Tissues which are present ordinarily in certain standard definite patterns, and the development of which does not extend beyond the usual range of so-called normal size, may for unknown reasons take on accelerated and excessive growth in mass. Other types represent overgrowth of tissues that have, so to speak, run wild. They grow rapidly and without restraint. Cells from such masses become separated, are carried away by blood or lymph and grow freely, forming new masses or metastases in any new locations in which they may happen to come to rest.

For example, the growing layer of the outer skin or epidermis may project deep down into the supporting tissues, forming non-vascular masses very much larger than the usual proportions. It is as though some overstimulative agency were acting on the growth process in absence of adequate inhibiting or restraining agency. Such overgrowth of epidermis or other tissue in effect becomes parasitic on the rest of the body, destroying the balance in development as between it and the normal tissues. This is in general the history of malignant or cancerous growths of whatever type and whatever origin.

In spite of enormous financial expenditure and scientific energy given to the solution of the cause of cancerous overgrowth, the causative facts are still unknown. In some tissues cancerous growths seem to start as a result of prolonged and repeated stimuli, either mechanical, or chemical, or combinations of the two. Once free from the restraint of the inhibitive processes, growth is rapid, voluminous, and destructive.

Summarizing this chapter we may emphasize the following:

1. Growth as a physiological process is dependent upon some deep, inherent characteristic of living protoplasm at present unknown. It is aptly described as "the growth impulse." An abundance of food and an adequate supply of vitamins provide the essentials for growth.

2. There are many organs, small in size but vital in importance, within the body of man and higher mammals, called endocrine glands, which secrete chemical hormones that profoundly influence the rate and character of growth activity by a process of augmentation or retardation. The average growth is therefore the algebraic sum of the stimulating and inhibiting processes going on within the body at all times during the life cycle.

3. Variations in the growth curve, typical for various species and man, depend largely on variations in the relative rate of production of the different stimulative and inhibitive hormones. This is coincident with the fact that internal secreting glands

differentiate or develop to a maximum and retrogress each by an independent curve of its own. Hence the sum of the hormonal influences varies from period to period in the life cycle.

4. When for any reason there is a profound augmentation, or an extreme decrease in the amount, of any particular internal secretion, the result on the body as a whole will be the production of an abnormal curve of growth. These abnormalities may range from the extreme amazonian stature of gigantism to the pigmy in dwarfism, from the slender, nervous, and cadaverous body of the hyperthyroid to the overfat and infantile form of pituitary distrophy, from the masculine and bearded form of the woman with adrenal tumor to the atrophy and retarded nervous and physical development of the congenital cretinous hypothyroid.

5. A certain amount of activity and normal degree of physiological fatigue favors a healthy energetic body and its processes of growth. Lethargy is unfavorable since the stimulus to physiological compensations is lacking. Overfatigue and exhaustion are destructive to vitality, injure the tissues, debase metabolism, and retard growth.

6. Finally, there are the perverted growths derived from various tissues and organs and which are entirely outside the range of orderly physiological variation of organ form or bodily development. These are the pathological tumors, either benign or pathogenic in nature, which produce extreme deviations or distortions in growth types. In fact, bodies with such perverted form are never taken into consideration in the usual measurement and study of growth processes, or in the construction of growth curves. The extremes of these types, the malignant cancers, when unrestrained by artificial methods lead quickly and directly to the destruction and death of the individual.

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Chapter II

This address is a summary of several papers published by the writer and associates in the *Journal of General Physiology*, and in a series of bulletins of the University of Missouri Agricultural Experiment Station at present in press under the the general title of "Growth and Development." *Research Bulletin 96* of the series contains a fairly complete bibliography on the time relations of growth and senescence. *Research Bulletin 97* discusses in detail the significance of growth curves and the method of fitting the given equations to data on the course of growth and senescence. *Research Bulletin 98* is concerned with the self-accelerating phase of growth. *Research Bulletin 101* is concerned with the self-inhibiting phase of growth, and *Research Bulletin 102* is concerned with equivalence of age.

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